THE EFFECTS OF ANÆSTHESIA AND ELECTIVE SURGERY ON OLD PEOPLE

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FOR many years reports have appeared of dementia in elderly patients after anæsthesia and surgery (Savage 1887, Turville and Dripps 1947–48), Bedford 1955, Papper 1956). Sometimes there is no history of a specific responsible incident, and a factor inherent in the anæsthetic has been suggested as a possible cause of this dementia (Savage 1887, Batten and Courville 1940, Turville and Dripps 1947–48, Lucas 1950, Cole 1953, Bedford 1955). Because of these reports and because many doctors can point to a patient, relative, or acquaintance who " has never been the same since operation ", surgeons and general practitioners may have been reluctant to recommend surgery in the elderly except in " unequivocally necessary cases " (Bedford 1955). We therefore undertook a survey to establish the amount of deterioration occurring after anæsthesia and elective surgery in an unselected group of elderly patients, and to gain information as to its cause. Particular attention was paid to the possibility that anæsthesia contributed to any deterioration which occurred.

Method

General

We decided that the degree of social integration of all patients aged 65 and over, admitted in 1959 for elective surgery to the United Oxford Hospitals (with the exception of the neurosurgical unit), should be assessed at home before admission to, and after discharge from, hospital. In addition, as many as possible of these patients should be submitted to a series of mental tests, before and after admission. The investigation was limited to patients undergoing elective (i.e., not emergency) surgery, so that preoperative assessment could provide a basis for comparison. We are not aware of any information as to the amount of deterioration which can be expected, over a similar period, in a similar group of old people not admitted to hospital. Any deterioration which occurred has been assumed to have arisen as a result of the patient's stay in hospital.

All the surgeons of the United Oxford Hospitals gave permission for patients under their care to be included in this survey, and we gratefully acknowledge their encouragement. 251 general practitioners in the Oxford region gave permission for their patients to be visited at home. The names of patients were obtained from the hospital's waiting-list, and the letter notifying admission was accompanied by a note preparing the patient for a visit from one of us (B. R. S.).

Pre-admission Assessment

All the patients were visited by B. R. S., and details of their physical activity, mental ability, personality, and general social integration were assembled. The answers to standardised questionnaires * put to each patient (and where possible, to a relative or friend) were recorded, and individual characteristics were elucidated by further questioning. These interviews lasted about half an hour. The patients were also submitted to the Tooting Bec Questionnaire (Doust et al. 1953)—a series of questions which has been found to provide as good a measure of dementia in older people as many more complex tests (Cosin et al. 1957).

This preoperative interview, by provoking some reflection on the patient's state at that time, both by himself and by his relative, drew attention to any already established change and prevented its being subsequently attributed to a particular event, such as the removal of the patient to hospital or any part of the treatment received there.

The information thus obtained about the patient's physical activity, mental ability, and personality was divided into six functions, each of which was scored on a five-point scale ranging from full (i.e., unaltered) function (grade 1) to severe deterioration (grade 5) (table I). The severity of the symptoms referable to the condition which required surgery was also scored on a five-point scale, and any change in symptoms after operation was also recorded and scored.

Pre-admission Mental Tests

Patients whom we believed would be most susceptible to deterioration—those to be subjected to major surgery and those in the older age-groups—were also visited before and after operation by a psychologist (M. W.) who gave them two parallel sets of mental tests. Long and exhaustive tests are unsuitable for old people (Welford 1958a and b). The full Wechsler and Raven Matrices tests each take about an hour and do not include tests of delayed memory recall and manual dexterity. They were replaced by selected procedures found by experience (Williams 1958) to be more suitable.

Record of Progress in Hospital

The anæsthetists of the United Oxford Hospitals completed a record card for each of the patients during anæsthesia, which included duration of anæsthesia, drugs used, blood-pressure, an estimate of blood loss and replacement, and also an account of any untoward incident. Any evidence of postoperative confusion was recorded by the ward sister, and one of us (B. R. S.) visited the surgical wards each week to obtain a progress report on each patient.

* Copies of the scoring sheets and questionnaire may be had from THE LANCET Office, 7, Adam-street, London, W.C.2.

TABLE I—SCORE SHEET

Function		Grade 1	2	3	4	5
Physical Activity	Self help	Independent Helps others	Maintains share of responsibilities	Looks after self but responsibilities reduced	Looks after self minimal help in running home, &c.	Cannot cope with self maintenance
	Degree of activity	Active as ever	Active but doing less in recent years	Slowed. Maintains activity with frequent rests	Mostly rests but capable of some activity	Bedridden or dependent on aid for movement
Mental Ability	Mental occupation	Occupied in constructive work	Partly occupied in constructive work but less than formerly	Passively occupied. Some outside interests	Limited passive occupation only	Sits and thinks
	Memory	Unchanged	Not quite as good	Increasing forgetfulness	Considerable change	Fragmentary recall only
Personality	Social relationship	Stable	Somewhat withdrawn. Inclined to worry and suspicion	Worries over trivialities. Timid	Suspicious, surly, vindictive, withdrawn	Out of contact with reality
	Emotional state	Well balanced	Occasional irritability or depression	Quick tempered. Frequent mood swings	Depressed most of the time. Uncontrolled mood swings	Apathetic

Post-discharge Assessment

Mental tests were usually repeated (using an alternative but standardised set of tests) two weeks after the patient's discharge. About three months after discharge the patients were revisited by the anæsthetist, and a comparison was made with pre-admission physical activity, mental ability, personality, and general social integration. Findings were recorded on questionnaires similar to those used at the preoperative interview, and the patients were scored by the method described (table I). Any patient showing deterioration was revisited on further occasions to estimate recovery or further deterioration. The whole investigation entailed travelling 33,000 miles (fig. 1).

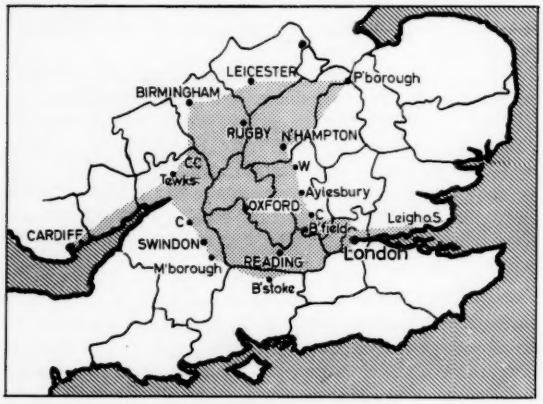

Fig. 1—Geriatric survey 1959.

Statistical Analysis

The information gathered from each patient was presented for statistical analysis (J.S.) in a form delineating thirty-eight variables. These were:

1. Age, sex, occupation, days in hospital, malignant or non-malignant lesion.
2. Anæsthetic used, if any.
3. Six measures of function (table I), and the change in each after discharge from hospital.
4. The score in the Tooting Bec Questionnaire before and after operation.
5. Preoperative symptom score—grades 1–5.
6. Postoperative symptom change score—grades 1–5.
7. Sixteen variables derived from mental test scores.

These variables were analysed by means of multiple regression equations. The regression equation establishes what effect any variable has on another single variable, if all the other variables likely to affect the first are held constant. For instance, the effect of anæsthesia on mental ability can be assessed while excluding the effect of other factors, such as age, sex, and postoperative symptom-change score.

By breaking down the composite picture of social integration into components, such as physical activity, mental ability, and personality (table I), and from the results of mental tests, we could ascertain the effect of anæsthesia on each of these components.

In the regression equation the variable for anæsthesia was coded by the scheme: 0 for no anæsthetic, 1 for local anæsthesia, and 2 for general anæsthesia. Thus all the patients contributed in determining the effect of anæsthesia. Expressed in another way, the "general anæsthetic" group was compared for a possible effect against the "local" group and the "no anæsthetic" group, the groups being adjusted for differences in all the other variables. (Age, sex, etc.). We would emphasise the fact that in this series "local anæsthesia" included spinal,

TABLE II—POSTOPERATIVE CHANGE OF SOCIAL INTEGRATION

Anæsthetic	Total	Much improved existence	Improved existence	Same existence	Limited existence	Much limited existence	Dead
General	472 (63·7% of total)	62 (13·1%)	100 (21·2%)	210 (44·5%)	35 (7·4%)	24 (5·1%)	41 (8·7%)
Local	206 (27·8% of total)	6 (2·9%)	55 (26·7%)	98 (47·5%)	23 (11·2%)	7 (3·4%)	17 (8·3%)
No anæsthetic	63 (8·5% of total)	0	5 (8·0%)	43 (68·2%)	9 (14·3%)	4 (6·3%)	2 (3·2%)
Total..	741	68 (9·2%)	160 (21·6%)	351 (47·4%)	67 (9·0%)	35 (4·7%)	60 (8·1%)

extradural, and extensive regional analgesia for major surgical procedures.

Method of Presenting Results in Terms of Change in Social Integration

From the point of view of those responsible for recommending surgery for old people our most relevant findings will be the change in measures of function after the patient's discharge from hospital (table I). To present these findings, the patients have been divided into groups related to changes in social integration. Patients who moved up one or two grades on our scoring system (table I) are described as living an "improved existence" and those who moved three or more grades as living a "much improved existence"; patients showing corresponding deterioration are described as living a "limited" and "much limited" existence (table II).

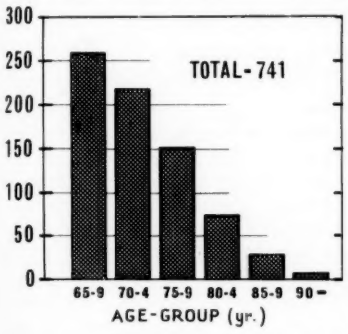

Fig. 2—Age distribution of the patients studied.

All patients who showed a change in social integration have been further studied and divided into groups to reveal the reasons for improvement or deterioration. The patients who died have been similarly classified to show reasons for their deaths.

Results

The investigation was carried out on 741 patients, and we believe these are all who were admitted to the United Oxford Hospitals in 1959 under our terms of reference. They were aged 65 or over, and the age distribution is shown in fig. 2. 60 died in hospital or before being revisited. For various reasons it was not possible to visit 65 of the patients in their homes before operation, but they were assessed preoperatively in hospital. 7 patients were not interviewed until after operation, but have been included. All but 3 of the survivors (who had moved prohibitively far from Oxford) were interviewed after discharge, and in these 3 cases the opinion of a relative who had been in close contact with the patient after operation was available.

TABLE III—NUMBER OF PATIENTS WITH GIVEN CHANGE IN SELF-HELP SCORE FOR VARIOUS ANÆSTHETICS

Anæsthetic	+3	+2	+1	0	−1	−2	−3	−4	Total	Mean change
General	4	10	39	340	28	10	..	..	431	+0·053
Local	..	4	13	161	10	1	..	..	189	+0·048
None	..	..	..	54	5	1	..	1	61	−0·181
Total no.	4	14	52	555	43	12	..	1	681	

TABLE IV—NUMBER OF PATIENTS WITH GIVEN CHANGE IN PHYSICAL-ACTIVITY SCORE FOR VARIOUS ANÆSTHETICS

Anæsthetic	+3	+2	+1	0	−1	−2	−3	Total no.	Mean change
General	1	12	68	313	32	5	..	431	+0·122
Local	..	2	22	149	16	..	..	189	+0·053
None	..	..	2	47	8	3	1	61	−0·246
Total no.	1	14	92	509	56	8	1	681	

TABLE V—NUMBER OF PATIENTS WITH GIVEN CHANGE IN MENTAL-ACTIVITY SCORE FOR VARIOUS ANÆSTHETICS

Anæsthetics	+2	+1	0	−1	−2	−3	Total no.	Mean change
General	9	32	369	16	5	..	431	+0·056
Local	4	20	157	7	1	..	189	+0·101
None	..	2	54	3	1	1	61	−0·098
Total no.	13	54	580	26	7	1	681	

Of the 741 patients investigated as above, 250 were subjected in addition to mental tests both before admission to hospital and two to four weeks after discharge from the surgical wards.

472 patients had general and 206 had local anæsthetics, administered by anæsthetists whose experience ranged widely. 63 of the 741 patients had neither anæsthetics nor operation, and were discharged after investigations or conservative treatment.

Effect of Anæsthesia

The primary object of this survey was to establish the relation between anæsthesia and any deterioration in a patient's general social integration after his return home from hospital, and particularly, the part played by anæsthesia in producing what Bedford (1955) called "lesser" or "extreme" degrees of dementia.

TABLE VI—NUMBER OF PATIENTS WITH GIVEN CHANGE IN MEMORY FOR VARIOUS ANÆSTHETICS

Anæsthetics	+2	+1	0	−1	−2	Total no.	Mean change
General	1	12	405	12	1	431	0
Local	..	..	185	4	..	189	−0·021
None	..	..	60	1	..	61	−0·018
Total no.	1	12	650	17	1	681	

The statistical analysis (J.S.) of our data involved the regression analysis of 40,000 observations and was made practicable by a Ferranti 'Mercury' computer. It established that anæsthesia had no effect on the physical activity, mental ability, personality, or social integration of the patients studied (tables III–VIII). There was no correlation between anæsthesia and the movement of patients up or down any of the measuring scales of any of the variables submitted for analysis.

Control Series: Effect of Stay in Hospital

The only control group available comprised the patients who were discharged from hospital or died without having had an operation or an anæsthetic. In table II these patients are divided into groups, showing the numbers who improved, remained the same, deteriorated, and died after admission to hospital. It will be seen that there is a general tendency towards deterioration, and this is repeated in the individual scores for social integration of this group of patients (tables IV–IX). In comparison, patients who had anæsthesia and elective surgery showed, in general, considerable improvement in social-integration scores.

TABLE VII—NUMBER OF PATIENTS WITH GIVEN CHANGE IN SOCIAL-RELATIONSHIP SCORE FOR VARIOUS ANÆSTHETICS

Anæsthetic	+3	+2	+1	0	−1	−2	−3	Total no.	Mean change
General	1	7	53	348	16	3	3	431	+0·090
Local	0	3	13	162	11	0	0	189	+0·018
None	..	..	2	55	3	..	1	61	−0·066
Total no.	1	10	68	565	30	3	4	681	

Minor Supplementary Findings

For an equivalent amount of symptom relief, the longer the patient's stay in hospital the less likely he was to improve in social integration after discharge. When improvement occurred, this was manifest in older patients by increased emotional stability rather than by increased physical activity. Patients in the higher grades of the Medical Research Council's (1944) " occupational classification ", for a similar degree of symptom relief, tended to improve more than patients in lower grades.

Major Supplementary Finding

There was a highly significant statistical correlation between the " postoperative symptom-change score " and the score indicating change in social integration (table IX);

TABLE VIII—NUMBER OF PATIENTS WITH GIVEN CHANGE IN EMOTION SCORE FOR VARIOUS ANÆSTHETICS

Anæsthetic	+3	+2	+1	0	−1	−2	−3	−4	Total no.	Mean change
General	1	24	132	245	23	3	2	1	431	+0·334
Local	..	5	47	120	13	4	..	..	189	+0·190
None	..	..	5	48	6	1	1	..	61	−0·098
Total no.	1	29	184	413	42	8	3	1	681	

in other words, of patients who had operations which relieved symptoms, many lived fuller lives, and of patients who had operations which did not relieve symptoms (or even created new symptoms) many lived more restricted lives. It is clear that, provided symptoms were relieved, the severity of the operation was immaterial to the outcome. Some of the most dramatic improvements followed the most serious operations, and deterioration sometimes occurred after relatively minor surgical procedures (table X).

This finding is, we believe, of such importance to those who have to advise on surgical problems in old people, that the case-histories of the patients in the groups in table II, and especially those who deteriorated, were examined more closely in an attempt to find reasons for the variations in postoperative behaviour.

TABLE IX—CORRELATION COEFFICIENTS RELATING POSTOPERATIVE SYMPTOM CHANGE SCORE WITH FACTORS COMPOSING SOCIAL INTEGRATION

Self help	Physical activity	Mental activity	Memory	Social relationship	Emotion
+0·522	+0·631	+0·499	+0·192	+0·519	+0·669

$P < 0.001$. These correlations are highly significant.

Reasons for Variation

Patients " Improved " or " Much Improved " after Elective Surgery

223 (33%) of patients lived an " improved " or " much improved " existence after elective surgery and anæsthesia. These patients could be divided into three groups.

Improved as a direct result of surgery.—205 patients fell into this group. An impressive example of a patient who had a " much improved existence " after elective surgery was one whose scores improved by three grades (table I).

He is a 65-year-old foreman in a building works who is also secretary of the local branch of the British Legion. He had had increasingly severe indigestion for many years. Fear of pain had restricted his eating for two years and he slept badly in the upright position enforced on him. For two years his performance in his various activities had been falling off appreciably. After repair of a hiatus hernia under general anæsthesia, he said he felt twenty years younger. He found his job much easier and he was paying more attention to it. Before operation " all sorts of people were helping with the organisation of the ' Legion ', because I could not cope—now I have taken control of the whole thing." His wife stated that many people had remarked that her husband seemed to be a new man.

Improvement not directly related to surgery.—8 patients fell into this group. The group included patients who, while improving as a result of surgery, also improved as

TABLE X—OPERATIONS AND CHANGES IN SOCIAL INTEGRATION

Groups of operations	Anæsthetic	No.	Level of postoperative social integration					
			Much improved	Improved	Same	Limited	Much limited	Dead
Major abdominal (gastrectomy, cholecystectomy, hiatus hernia, resection of colon or rectum, nephrectomy, cystectomy, prostatectomy)	General	148	39	48	37	8	4	12
	Local	9	2	..	5	..	..	2
Laparotomy (condition found inoperable)	General	9	..	..	..	2	2	5
Minor abdominal (appendectomy, hæmorrhoidectomy, &c.)	General	13	..	3	10	..	..	..
	Local	3	..	2	..	..	1	..
Major gynæcological (total hysterectomy, vaginal hysterectomy, pelvic-floor repair, total vulvectomy)	General	22	3	12	6	1	..	..
	Local	12	..	5	5	2	..	..
Minor gynæcological (radium to cervix, dilatation and curettage, urethral caruncle)	General	12	2	4	4	..	1	1
	Local	1	..	..	..	1	..	..
Major E.N.T. (total laryngectomy, mastoidectomy, parotid tumours, &c.)	General	12	1	2	6	1	..	2
Minor E.N.T. (submucous resection, Caldwell-Luc, tonsillectomy, œsophagoscopy)	General	26	4	4	7	4	3	4
	Local	15	..	6	7	2	..	..
Major plastic (for malignant disease)	General	15	..	..	3	5	6	1
Major thoracic (pneumonectomy, lobectomy)	General	10	2	..	2	1	3	2
Major vascular (amputations, endarterectomy, arterial grafts, &c.)	General	15	1	8	2	1	1	2
	Local	2	..	..	..	1	..	1
Mastectomy (radical or local)	General	32	1	2	23	..	1	5
Thyroidectomy	General	3	2	..	1	..	..	..
Transposition of ulnar nerve	General	2	2	..	..	..	..	..
Miscellaneous (excision of tuberculous abscesses, bedsores, varicose ulcers, rodent ulcers, orchidectomy, circumcision, dentals)	General	88	3	11	60	8	2	4
	Local	8	..	4	4	..	..	..
Minor urinogenital (suprapubic cystotomy, cystodiathermy, cystoscopy)	General	65	2	6	49	4	1	3
	Local	47	..	2	30	5	3	7
Eye (cataracts, &c.)	Local	109	4	36	47	12	3	7
Total		678	68	155	308	58	31	58
No operation or anæsthetic:								
Admitted for conservative treatment of varicose ulcers		6	..	2	4	..	..	..
Admitted for investigation only		35	..	2	26	7	..	..
Decision after admission that condition was inoperable		7	..	..	3	1	1	2
Decision after admission that operation unnecessary		8	..	..	8	..	..	..
Patient did not come to hospital (decision after interview at home by B.R.S.)		7	..	1	2	1	3	..
Total		63	..	5	43	8	4	2

a result of treatment of coexisting conditions, such as heart-failure, anæmia, thyroid deficiency, or obesity.

An example is a man of 69 whose left inguinal hernia had gradually increased in size for ten years. He had not felt well for twelve months, complaining of increasing dizziness and irritability. Until four months before admission he had worked hard in a large garden and looked after a pony and a few fowls. He watched football each Saturday. During these four months pain from his hernia increased and his activities decreased until he " just sat around ". On admission for the repair of an enormous scrotal hernia he was found to have dribbling incontinence from prostatic hypertrophy. His hæmoglobin was 6·3 g. per 100 ml. and his blood-urea 253 mg/ml. After treatment during eighty-seven days in hospital, he was discharged with his hernia repaired and an indwelling Foley catheter. He gradually resumed all his former activities, and became his usual cheerful self. Prostatectomy is envisaged at a later date.

Miscellaneous.—10 patients fell into this group. 7 improved because of the removal of a source of worry without alteration in symptoms. 2 others became much more cheerful because of an improvement in their living conditions. The last patient, though her sight was not improved by operation for cataract, had quite a marked personality change by becoming aware of how many people were worse off than she.

Patients Who Remained the Same After Elective Surgery

The classification of 308 (46%) patients remained unchanged after elective surgery. This group was made up of patients who either had minimal symptoms, or whose symptoms were unaltered. The large number of patients who " remained the same " after anæsthesia and elective surgery is slightly misleading. In fact 93 of these patients led fuller lives, 157 " remained the same ", and 58 deteriorated slightly. This division has not been made in table II because, owing to the fact that the whole range of function from full to minimal must be spanned by five grades, unequivocal evidence of improvement or deterioration is necessary to move a patient from one grade to another (table I).

It was also observed that, among patients who had operations for conditions unlikely to cause major symptoms, the classification of the majority was uninfluenced by surgery—e.g., of 26 subjected to mastectomy (20 radical) 24 remained the same after operation. 2 who led fuller lives had been relieved of pain associated with their primary lesion.

Patients Living " Limited " or " Much Limited " Existence After Elective Surgery

89 (12%) of all the patients were found to lead " limited " or " much limited " existences after elective surgery (table II). This at first appears inconsistent with our impression of overall benefit, and seems to be an unacceptably high proportion of patients to put at risk. The 89 patients fell easily into four groups.

Patients who deteriorated because of disease processes unconnected with the condition for which surgery was undertaken.—35 patients fell into this group. 20 had general anæsthetics and 15 local anæsthetics. A typical case is:

A severe arthritic, aged 72, had a pelvic-floor repair under spinal analgesia. Three months after operation she said that the " dragging pain in the back ", which previously had sometimes enforced a day in bed, was greatly relieved, but that her " arthritis " had been much worse since discharge from hospital, and the resulting limitation of her usefulness had caused her to feel, as she said, " very low-spirited ". She was, in fact, doing less housework and gardening, and where she had previously read two or three books each week, she now read only the newspapers. She was also subject to more frequent periods of depression.

Patients who deteriorated as a result of an increase in symptoms for which surgery was undertaken.—50 patients fell into this group and of these 38 had general anæsthesia and 12 local. In many cases the deterioration was inevitable, as when laparotomy revealed an inoperable carcinoma. In others, however, deterioration occurred because of the failure of surgery to achieve its purpose. This subgroup must be regarded with reserve because it includes patients in whom the malignant nature of their disease justified surgical intervention to spare them an even worse fate.

A woman of 69 had five operations in 1958, including a total hysterectomy for carcinoma of the body of the uterus, without noticeable deterioration. Later, after radiotherapy, she developed an ulcerated area on her back and a tender anterior abdominal wall. In 1959 an attempt was made to swing flaps of skin from the lateral aspects of her hips to close the ulcer on her back. On her return home, after a hundred and five days, the grafts had not taken, and the source areas had failed to heal. This lady, while by no means our most active subject, had previously taken part in various activities: she washed up, she read a book each week, she enjoyed the company of her grandchildren. When reinterviewed three months later she was found rocking to and fro in a chair because the areas on her back, abdomen, and hips made it impossible to achieve any degree of comfort in any other position. Her modest activities, both physical and mental, had come to an end. Her own description of her memory was that it was " shot ". Her grandchildren, previously her pride and joy, were ignored: in her own words, " I don't take no interest in anything." Her relatives confirmed her statements.

Patients who deteriorated from organic cerebral damage.—This " group " consisted of the only patient judged to have suffered organic cerebral damage.

A man aged 72 worked as a sweeper until the day he was admitted to hospital in 1959. He had had, in 1957, a conservative resection of rectum, from which he made an excellent recovery and returned to work. In 1959 sigmoidoscopy revealed a carcinoma of colon and abdominoperineal resection was performed. Before readmission his various simple interests included visiting the public-house and " doing the pools ". On the first postoperative day he received two doses of morphine 10 mg. to control pain, and his response suggested that this was excessive. The same night, therefore, the house-surgeon reduced the dose of morphine to 5 mg. but added 200 mg. of phenobarbitone intramuscularly. An hour after the dose of phenobarbitone the patient was restless and confused, and pulled out his urethral catheter. He remained confused throughout the following day and received two doses of 5 ml. of paraldehyde intramuscularly. As the restlessness continued, he was given amylobarbitone sodium 400 mg., after which he slept for twenty-four hours. When he was discharged eighteen days later, the ward sister thought him still slightly confused. When visited at home three months later he had not returned to work, and was physically less active. His interests were fewer, he rarely visited the public-house, and could no longer concentrate enough to finish anything which he started. His wife supported these findings. Unfortunately he was not in the subgroup of patients subjected to preoperative mental tests.

Patients who deteriorated without a satisfactory explanation.—Of the 3 patients in this group, 1 had a general anæsthetic and 2 had minor local anæsthetics. The deterioration was in no case more than moderate. One patient, for example, complained of some impairment of

memory and a " feeling that things got more on top of her ".

The deterioration in the last two groups can easily be distinguished from that of a progressive ageing or disease process by the fact that in each case the " dip " in performance was sudden, related to the patient's stay in hospital, and that there was no improvement or further deterioration on re-checking, in 1 case as late as one year after operation.

Our evidence thus suggests that when patients submitted to elective surgery deteriorate after operation, the great majority do so for identifiable reasons, which are not due to organic cerebral damage and which are unrelated to the anæsthetic agents used.

Patients who died after anæsthesia and elective surgery.—60 (8%) patients died, 58 after anæsthesia and elective surgery, and 2 after admission to hospital without operation. The present paper principally refers to the survivors of elective surgery, and we therefore comment only briefly on those who died:

41 patients had general anæsthesia. All of them emerged normally from anæsthesia and none showed any evidence of organic cerebral damage immediately after operation. These patients fell easily into four groups: 21 patients died from ageing or disease process unconnected with the condition for which surgery was undertaken; 25 died from progress of the disease process for which surgery was undertaken; 7 died from surgical mishap; and 7 patients died in the postoperative period from chest complications including acute pulmonary embolism.

Although a death-rate of 8% appears unacceptably high, the number of patients whose deaths were directly due to surgical intervention is as low as 14 or 2·2% of the total, and this disregards patients who would have died without surgical intervention.

It can thus be said of those patients who died, as well as of the survivors who deteriorated, that they did so for identifiable reasons not due to organic cerebral damage and unconnected with the anæsthetic agents used.

Discussion

If the clinical impression of deterioration in some patients after anæsthesia has any real basis, personal observation supplemented by formal mental testing should establish the size of the problem.

The battery of mental tests designed for this investigation have been discussed elsewhere (Williams 1960): they revealed no evidence of deterioration in basic mental ability in any of the 250 patients subjected to them in this series. Because of the limitations of mental tests, however, minor degrees of mental impairment may have passed unnoticed. If so, they were too small to be apparent to the patient himself, a relative, or an anæsthetist. We encountered 6 patients in this series each of whom had had general anæsthesia and surgery more than twenty times, for conditions such as papillomata of the bladder, after reaching the age of 65, without any evidence of deterioration.

Deterioration in social integration did occur in some of these 250 patients after anæsthesia and elective surgery, so it follows that mental ability and social integration are not necessarily to be equated. Many factors, apart from change in basic mental ability, may modify the patient's social integration on return to the home environment, and prominent among these is any alteration for better or worse in the patient's general sense of wellbeing.

The stimulus which resulted in the survey under discussion was a paper by Bedford (1955) in which are described 18 cases of gross dementia occurring after anæsthesia and surgery, and also a number of patients who " had never been the same since operation ", and who are described as showing " lesser degrees of dementia ".

No patient in our present series showed gross dementia, and a number of factors may have contributed to this difference. One is that our survey was conducted after Bedford's paper had been published, and the anæsthetists concerned, who knew that it was in progress, were even more aware than most anæsthetists of the implications of Bedford's findings. Bedford's material included emergency operations, which have been shown (Cutler 1947, Bosch et al. 1952, Glenn and Hays 1955) to carry a higher incidence of all complications than operations of election; the present survey is confined to elective surgery. The survey was undertaken five years after Bedford's was complete, and advances in all phases of patient care have been made, even in this comparatively short time. For instance, the extreme dementia described by Bedford was manifest on recovery from anæsthesia, but whereas this potentially dangerous period of recovery (Macintosh 1954) was often protracted in 1949–54, by 1959 the patient usually recovered in the operating-theatre while still under the care of the anæsthetist.

Other improvements in the care of surgical patients which may have contributed to the absence of gross dementia in our series, are the earlier and more energetic correction of biochemical imbalance (Beling et al. 1952), more extensive practice of early ambulation (Leithauser 1943), more general use of blood-transfusion (Graham-Stewart 1960), and realisation of the dangers of Fowler's position (Bourne 1957, Macintosh 1960), together with an increased awareness that morphine, hyoscine, and barbiturates are not without risk in elderly patients (Bedford 1955).

The patients in Bedford's series who displayed " lesser degrees of dementia " appear to have much in common with the patients in our series who lived " limited " or " much limited " existences. The incidence is similar, and the tenor of the relatives' allegations was the same in both series. In our survey, of the patients who led " limited " or " much limited " existences, none of the 37 who were subjected to formal mental testing showed any change in basic mental ability, and all but 4 (2 of whom had local anæsthetics) of the 681 survivors showed good reasons for deterioration, unrelated to anæsthesia or to organic cerebral damage.

It is tempting to assume that a study of those patients in Bedford's series who showed " lesser degrees of dementia " might have revealed an equal number of good reasons for their deterioration.

The statistical analysis of our results confirmed our clinical impression of the overall benefit of elective surgery to old people, and is considerably more encouraging to those who have to accept the responsibility for recommending surgery for old people than were the results of many previous surveys. There seems to be no justification for denying surgery to old people because of a risk inherent in the drugs used in anæsthesia. Nevertheless the reduction of reserves in old people (Ausherman 1955, Wilson 1955, Whittenberger 1956, Zeman 1957, Welford 1958a and b) not only decreases the margin of error permissible to the anæsthetist but also increases the penalties

for even minor shortcomings in patient care. Neither the drugs used during anæsthesia, nor anæsthesia in its widest sense did any harm to the patients studied in this series; but the evidence of Bedford (1955) confirms that disaster can follow inadequate care during anæsthesia, or in the dangerous period of recovery (Macintosh 1954).

In the same way severe penalties are exacted for imperfections in surgical care. Minor departures from physiological normality, for which the younger patient can easily compensate, may jeopardise recovery in older people. The results of surgery may thus be less favourable in older than in younger age-groups, but the reasons for results short of the ideal in this series were almost always identifiable and often avoidable. The benefits of successful surgery in old people are often so dramatic that the additional difficulties involved must be regarded as a challenge to anæsthetist and surgeon, and not as grounds for restricting operations to " unequivocally necessary cases " (Bedford 1955).

Finally, it is hoped that the results of this series will encourage earlier recourse to elective surgery and so avoid the well recognised additional risks of emergency surgery which are especially evident in old people.

Summary

The degree of social integration of 741 patients aged 65 or over admitted to the United Oxford Hospitals for elective surgery in 1959 was assessed at home before and after operation. This assessment was supplemented by mental testing before and after operation in 250 of these patients.

Anæsthesia had no effect on the physical activity, mental ability, or personality of the patients investigated.

Statistical analysis of results confirmed a clinical impression of the overall benefit of elective surgery to old people as reflected by improvement in social integration. Where deterioration occurred, good reasons for it could be found which were unrelated to anæsthesia or to organic cerebral damage.

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REFERENCES

Ausherman, H. M. (1955) *Sth. med. J., Nashville*, **48**, 130.
Batten, C. T., Courville, C. B. (1940) *Anesthesiology*, **1**, 261.
Bedford, P. D. (1955) *Lancet*, ii, 259.
Beling, C. A., Bosch, D. T., Carter, O. B., Jr. (1952) *Geriatrics*, **7**, 179.
Bosch, D. T., Islami, A., Tan, C. T. C., Beling, C. A. (1952) *Arch. Surg.* **64**, 269.
Bourne, J. G. (1957) *Lancet*, ii, 499.
Cole, W. H. (1953) *Ann. Surg.* **138**, 145.
Cosin, L. Z., Mort, M., Post, F., Westropp, C., Williams, M. (1957) *Int. J. Soc. Psychiat.* **3**, 195.
Cutler, C. W., Jr. (1947) *Ann. Surg.* **126**, 763.
Doust, J. W. L., Schneider, R. A., Talland, G. A., Walsh, M. A., Barker, G. B. (1953) *J. nerv. ment. Dis.* **117**, 383.
Glenn, F., Hays, D. M. (1955) *Surg. Gynec. Obstet.* **100**, 11.
Graham-Stewart, C. W. (1960) *Lancet*, ii, 421.
Leithauser, D. J. (1943) *Arch. Surg.* **47**, 203.
Lucas, B. G. B. (1950) *Proc. R. Soc. Med.* **43**, 606.
Macintosh, R. R. (1954) *Rev. esp. Anestesiol.* **1**, 97.
— (1960) *Brit. Dent. J.* **109**, 257.
Medical Research Council (1944) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 248; p. 153.
Papper, E. M. (1956) *Bull. N.Y. Acad. Med.* **32**, 635.
Savage, G. H. (1887) *Brit. med. J.* ii, 1199.
Turville, C. D., Dripps, R. D. (1947–48) *Penn. med. J.* **51**, 434.
Welford, A. T. (1958a) Ageing and Human Skill; p. 49. The Nuffield Foundation, London.
— (1958b) *ibid.*, p. 4.
Whittenberger, J. L. (1956) *Bull. N.Y. Acad. Med.* **32**, 329.
Williams, M. (1958) *J. ment. Sci.* **104**, 783.
— (1960) *Brit. J. med. Psychol.* **33**, 215.
Wilson, T. S. (1955) *Med. Pr.* **234**, 373.
Zeman, F. D. (1957) *New Engl. J. Med.* **257**, 317.

POSTALCOHOLIC HYPOGLYCÆMIA AND TOXIC HEPATITIS

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IN the privileged communities of the world spontaneous hypoglycæmia is an infrequent cause of coma. For some years, however, it has been recognised as a more common cause of coma among African and, to a lesser extent, Indian patients at this hospital. A clinicopathological investigation of the causes of hypoglycæmia was therefore commenced. It soon became apparent that the commonest cause of spontaneous hypoglycæmia among adult patients was postalcoholic hypoglycæmia. The clinicopathological findings are described here.

Materials and Methods

Patients

21 Africans (16 male) and 2 Indians (1 male) were investigated, after admission in coma to King Edward VIII Hospital during the period February to December, 1960. Initial histories were obtained, wherever possible, from accompanying relatives. After clinical examination, blood was withdrawn for hæmatological and biochemical investigation. 50% intravenous dextrose solution was administered immediately after the blood had been withdrawn. A more detailed history was taken once the patients were fully oriented, and, where necessary, social workers investigated home circumstances. Liver biopsy was performed on 20 patients (3 of these on admission, while still in coma). Patients were kept in hospital until fit for discharge, and laboratory investigations were repeated daily in most cases. Necropsy was performed on 3 patients.

Biochemical Investigations

Blood-glucose (" true " blood-sugar), alkaline-phosphatase activity, and total bilirubin were estimated by standard routine laboratory methods (King and Wootton 1956). Blood volatile reducing substances were determined by the method of Bowden and McCallum (1949).

Serum-glutamic oxaloacetic-acid-transaminase (S.G.O.T.) activity was estimated by Hergt and Langin's (1957) simplified modification of the original method of Karmen et al. (1956). The measurements were carried out in an air-conditioned room at 23°C(±1°C). No temperature corrections were made.

Certain other investigations were undertaken. These included estimations of prothrombin index (Quick's method), zinc and thymol turbidities, serum-electrophoresis, blood-urea, serum-electrolytes, four-hour glucose-tolerance tests, chest X-ray, and a routine urine examination and blood-count. An electrocardiogram (E.C.G.) was obtained in the first 9 cases while serum-amylase was determined in the first 11, 17-oxosteroids and total urinary glucocorticoids were determined in 6 cases.

Clinical Findings

In every case a history of alcoholic intoxication on the day of admission or, more commonly, on the previous day or days was obtained. The majority had been drinking for years, but only 6 patients were considered to be chronic alcoholics. At least half were only heavy weekend drinkers. 1 of the patients was a child of 5 years, who accidentally drank alcohol. The dietary history of the African patients was poor, showing an intake, high in carbohydrate and low in protein and fat, characteristic of the African. Both Indians were on poor diet—1 as the result of a high alcohol intake.

TABLE I—ZULU BREWS AND DISTILLATE

—	Zulu beer	Shimeyane	Gavine
Ingredients	Mealie meal Corn malt Water	Brown bread Brown sugar Corn malt Yeast Water	Distillate of shimeyane
Alcohol content (%)	±3	3–6	30–50
Time taken in preparation	4–5 days	24 hours	..

19 of the Africans had been drinking Zulu beer, or shimeyane or gavine (African liquors), or a combination of all three, in alcohol debauches (see table I). Of the remaining patients, 2 had been drinking cane spirit, 1 brandy, and 1 gin. Most of the patients had not eaten for twelve to twenty-four hours prior to the drinking bout. 7 awoke on the morning after their alcoholic bout, but subsequently felt weak and lost consciousness. In these cases the interval between the end of the alcoholic bout and the onset of hypoglycæmic coma varied from eight to fifteen hours, while the interval between awakening and the onset of coma varied from minutes to two hours. These patients remained unconscious for eight to eleven hours before treatment was instituted. The remaining 16 patients retired to bed intoxicated and were admitted in a coma twelve to twenty-four hours later.

Physical Examination

Pellagrinous dermatitis was found in 5 patients and poor nutrition in 10. 4 patients had pulmonary tuberculosis. Body-temperature was usually subnormal, while sweating was noted in only 1 case. In the majority of cases the pulse-rate was normal or slightly raised, but in 2 the pulse was not palpable and the heart-rate was under 30 per minute. The blood-pressure was temporarily raised on admission in 6 and low in 5; in 2 of these 5 it was unrecordable. Respiration was normal in type, stertorous, or slow and shallow. 2 patients on admission were breathing at the rate of 5 and 6 per minute. The liver was tender in 2 cases and palpable in the majority, but in none was it grossly enlarged.

21 of the patients were in coma on admission. Of the remaining 2, in 1 there was mental confusion, aggressiveness, and incoherent speech; while in the other there was mild stupor, disorientation, and slurred speech. Coma was the only sign in 4 cases; but in others involvement of the central nervous system, often bizarre, was found. 5 patients had generalised convulsions. Symptoms found in other cases were twitching of an arm, facial palsy, hemiparesis, conjugate deviation of the eyes, spasticity, hypotonia, abnormal deep reflexes, clonus, and extensor plantar reflexes.

Diagnoses on admission included spontaneous hypoglycæmia, alcoholic coma, cerebrovascular accident, hypertensive encephalopathy, internal head injury, hepatic coma, grand-mal epilepsy, and postepileptic state.

Bronchopneumonia was an occasional complication, and was considered to be an aspiration pneumonia from inhalation of foreign material during the period of coma. In 2 patients delirium tremens developed two days after admission.

Treatment

All patients except 1 were treated by intravenous administration of 20–70 ml. 50% dextrose solution. 18 recovered immediately and completely and required no further treatment. 4 remained mentally abnormal for various periods. 1 patient was unable to speak for twenty-four hours (it was later ascertained that he had had a period of motor aphasia for about twelve hours and loss of memory before that). Another remained mentally abnormal and was able to say only a few words until her death eighteen days later. A 3rd patient was mentally dull for twenty-four hours and suffered from slurred speech for four days before complete recovery took place. In the 5-year-old child the level of consciousness improved after administration of intravenous dextrose solution, but he remained stuporose until he died sixteen hours later. 1 patient, who received no treatment, died a few hours after admission; the blood-sugar was later found to be 36 mg. per 100 ml.

Illustrative Case

An African man, aged 36 years, was admitted stuporose, coughing and smelling of stale alcohol. Pulse-rate 60 per minute; blood-pressure 110/60 mm. Hg. There were extensor plantars and flaccidity of all four limbs, but the deep tendon reflexes were normal. There were no other abnormalities. Postalcoholic hypoglycæmia was suspected. The patient responded immediately to intravenous administration of 35 ml. 50% dextrose solution. The blood-sugar proved to be 43 mg. per 100 ml.

After treatment the patient was found to have been drinking Zulu beer and brandy with a group of friends from 9 A.M. to 7 P.M. on the day before admission. He then retired to bed, having not eaten lunch or supper. At 5 A.M. on the following

TABLE II—BIOCHEMICAL FINDINGS ON ADMISSION*

Case no.	Blood-sugar (mg. per 100 ml.)	Volatile reducing substances (mg. per 100 ml.)	Bilirubin (mg. per 100 ml.)	Alk. phosph. (K.-A. units)	S.G.O.T. (Karmen units)	Prothrombin index	Urobilin
1	28	..	1·3 (4)*	14·0 (4)	172 (3)	86 (3)	–
2	35	..	0·9 (2)	11·0	82 (2)	100 (3)	+ (4)
3	25	..	–	12·0 (5)	96	74 (6)	Tr. (4)
4	28	..	1·5	22·0	98	74	+
5	44	..	–	15·0	130	79	+
6	42	..	–	32·0	128	79	Tr.
7	25	..	–	9·0	300	83	Neg.
8	13	..	–	11·0	276	74	Neg.
9	9	..	0·8	4·0	148	57	Neg.
10	27	..	4·3	12·0	–	78	+
11	20	6·0	0·5	11·0	60 (2)	72	Neg.
12	25	17·0	1·5	8·0	56	88	Neg.
13	20	76·0	1·0 (2)	12·0 (2)	150 (2)	73	+ + (2)
14	39	11·0	0·7	15·0	200	82	Neg.
15	36	Died on admission					
16	26	11·0	0·8	9·0 (2)	38	100	Neg.
17	33	12·0	0·8	15·0 (2)	150	100 (4)	Neg.
18	43	..	–	7·0 (2)	44 (2)	94 (2)	Neg.
19	23	28·0	0·4	15·0	550	35	Neg.
20	23	20·0	0·8	12·0	28	92	+ +
21	24	..	..	..	..	..	..
22	20	..	1·2	7·0	186	78	Neg.
23	47	..	0·4	7·0	336	91	Neg.

*Numerals in parentheses show number of days after admission on which test was done.

TABLE III—S.G.O.T. ACTIVITIES

Days	Case no.						
	5	7	9	12	16	23	18*
1	130	300	148	56	38	336	36
2	180	150	94	52	40	180	44
3	92	350	60	40	46	108	50
4	66	70	50	40	50	60	154
5	52	74	36	28	47	58	66
6	30	60	30	12	36	56	38
7	..	..	..	..	20	30	50
8	30	..	..	..	28	..	48
9	..	40	..	..	..	..	60
10	..	..	36	..	..	..	42

*Activities after administration of 100 ml. absolute alcohol.

morning he awoke and went to work by bus, reaching the factory at 6 A.M , when work began At 6.35 A.M., while using a machine, he felt giddy and had hot and cold flushes and cramp in the lower limbs. He gradually became confused. Within half an hour he could not operate his machine, nor could he do a light job which the foreman had given him. He then lost consciousness, and convulsions occurred. The employer considered that the patient was drunk and he was discharged from his job.

The patient said that he was a heavy weekend drinker and only drank in the company of his friends. He had worked at the same factory for eighteen months, and the records showed that he had been off work on only five days. He was regarded as a reliable and intelligent worker. He was happily married and had two children. The diet, on which only 25*s.* per week was spent, consisted mainly of maize products.

Biochemical Findings

Table II lists the blood-glucose concentrations and blood volatile reducing substance on admission, and the results of biochemical tests related to the functional integrity of the liver. From these results it is clear that the diagnosis of hypoglycæmia was not in doubt, while the volatile reducing substances were either within normal limits or, if raised, not anywhere near the levels found in alcoholic coma. The tests related to the functional integrity of the liver showed evidence of liver dysfunction.

As results obtained, on or after admission, in a group of patients reflect a scatter pattern of the disease process at various stages of development, daily examinations were carried out in order to obtain a clearer understanding of the natural history of the liver disorder. Table III shows the S.G.O.T. activities obtained daily in 6 cases, while table IV shows S.G.O.T. activities in a further 5 cases together with the total bilirubin, alkaline phosphatase, and urinary urobilin. On the evidence of these results, there can be little doubt that the liver disorder is a mild and transient hepatogenous jaundice. Tests related to the serum-proteins were not included in the table because of difficulties in interpretation of these results in African patients (Joubert et al. 1959).

In view of the histories obtained from the patients, an attempt was made, after recovery from the hepatogenous jaundice, to demonstrate the effect of a single administration of pure ethyl alcohol. A single dose of absolute alcohol (100 ml.), half-diluted with water, was administered to one patient. As the S.G.O.T. activity was clearly the most sensitive index of the liver disorder in the patients, it was followed over a number of days. The result is given in table III. Clearly, a relatively small dose of pure ethyl alcohol caused sufficient liver damage to result in an increase in S.G.O.T. activity.

The majority of glucose-tolerance tests performed showed mild abnormalities, the curves not returning to fasting levels at two hours. However, as the glucose-tolerance tests and, in addition, the tests associated with steroid metabolism were performed during recovery from the liver disorder, interpretation of the results is difficult and further investigation is necessary.

Liver-biopsy Findings

In 20 cases liver biopsy was performed. It was not possible to report on 3 of these because insufficient tissue was obtained. Of the remaining 17 biopsies, only 3 showed evidence of cirrhosis. The remaining 14 showed a normal architectural pattern. Fat vacuolation was not usually pronounced in sections stained with hæmatoxylin and eosin. Sufficient tissue was obtained for fat staining (Sudan III) in 4 cases. Fatty change was observed in 3 of these cases, and was absent in 1. In the 3 cases where liver biopsy was performed on admission, absence of glycogen was noted (Best carmine and periodic-acid/Schiff) while, in a case where the liver biopsy was performed an hour and a half after dextrose administration, minimal glycogen deposition was observed.

Necropsy

The only significant findings in the 3 necropsies were fatty liver in 2 cases and bronchopneumonia in 1. In 1 case, where no treatment had been given, glycogen was absent from the liver; but, as the necropsy took place sixteen hours after death, this is of doubtful significance.

Discussion

The established facts in this study may be summarised as follows:

1. Hypoglycæmic coma followed approximately twelve hours after a period of excessive drinking of alcoholic liquors.
2. Mild and transient hepatitis was demonstrated in all patients.
3. The hypoglycæmia was completely reversed by a single intravenous administration of 20–70 ml. 50% dextrose solution.

Five earlier published reports on postalcoholic hypoglycæmia were found.

The first report was published by Brown and Harvey (1941). They considered that their 6 patients had been drinking a liquor known as " smoke ", which contained certain additives (methyl alcohol, gasoline, and ethyl acetate). Tucker and Porter (1942) reported 4 cases. They suspected that their patients had been drinking a denatured alcohol, known as " solox ", the composition of which was the same as that of

TABLE IV—S.G.O.T., SERUM-BILIRUBIN, SERUM-ALKALINE-PHOSPHATASE, AND URINARY UROBILIN

Days	Case no.																			
	11				13				14				19				22			
	T.	B.	A.P.	U.	T.	B.	A.P.	U.	T.	B.	A.P.	U.	T.	B.	A.P.	U	T.	B.	A.P.	U.
1	..	0·5	11	Nil	..	..	12	++	200	0·7	15	Nil	550	0·4	15	..	186	1·2	7	Nil
2	60	1·3	..	Nil	150	..	..	+	126	0·8	..	Nil	260	0·4	13	Nil	62	1·8	7	+
3	104	1·6	..	++	90	1·0	..	+	102	1·2	..	+	124	0·4	11	++	60	0·7	5	Nil
4	110	0·5	..	Nil	90	2·0	..	+	40	0·4	2	+++	70	0·4	10	+++	44	0·4	6	Nil
5	70	0·5	..	Nil	32	0·8	..	++	32	0·5	..	+++	..	..	..	+++	40	0·6	6	Nil
6	78	0·3	4	Nil	..	0·8	..	Nil	20	0·2	..	+++	96	..	..	trace	50	0·6	6	Nil
7	..	..	..	..	..	0·6	..	Nil	18	0·2	..	++	90	..	..	Nil	20	0·4	..	Nil
8	44	..	..	..	20	..	..	..	..	..	..	++	66	..	..	Nil	..	..	..	..

T. = S.G.O.T. B. = Serum-bilirubin A.P. = Serum-alkaline-phosphates. U. = urinary urobilin. Nil = not increased.

" smoke ". In both these reports, the denatured alcohol was regarded as responsible for the hypoglycæmia.

Bottura et al. (1949) reported 11 cases which followed the intake of ethyl alcohol, and 20 cases were reported by Neves et al. (1950). All these patients, except 2 reported in the 1950 series, were considered to be chronic alcoholics.

Peluffo et al. (1958) reported 2 cases in children, 1 of whom showed obvious signs of malnutrition. Taylor (1955) reported a case of hypoglycæmic coma in a chronic alcoholic. There was, however, no admission of antecedent alcohol excess.

All the cases in the present series must be regarded as examples of postalcoholic hypoglycæmia. The majority of these patients had, owing to the liquor laws relating to Africans in this country, been drinking " illicit " liquor. Because of this, the possibility of toxic additives (Brown and Harvey 1941, Tucker and Porter 1942) was considered. No such history was obtained from any of the patients; nor did there seem to be any necessity for their withholding this information, as many had already admitted to drinking gavine and shimeyane. The majority of the patients were drinking in social groups, other members of which were unaffected; and some of the patients had been drinking only gin, cane spirit, or brandy. In addition, administration of ethyl alcohol itself resulted in S.G.O.T. activity similar to that found in these patients. Thus we believe that ethyl alcohol was the toxin concerned and that hypoglycæmia and toxic hepatitis resulted from its intake.

Bang et al. (1958) and Hed (1959), studying transaminase activity in chronic alcoholics after acute alcoholic intoxication, found similar S.G.O.T. levels to those reported here. In a further study of chronic alcoholics, Madsen et al. (1959) emphasised the role of prolonged and inadequate dietary intake in the production of abnormal S.G.O.T. activity following acute alcoholic intoxication. In their group a poor diet resulted from chronic alcoholism, where alcohol was used as the main source of calories. The majority of the patients reported here could not be termed chronic alcoholics; but, on the other hand, there had been a poor dietary intake for years as a result of poverty and of the dietary habits of the African. Thus we believe that it was the long-continued inadequate intake that resulted in the liver being vulnerable to mild toxins, such as ethyl alcohol. The ultimate result of frequent liver insults of this nature may be cirrhosis. It is noteworthy that there was no corresponding histological lesion on liver biopsy.

In regard to the mechanism of the hypoglycæmia, Brown and Harvey (1941) considered that, in their cases, the postalcoholic hypoglycæmia resulted from inhibition of gluconeogenesis, owing to the additives. Tucker and Porter (1942) supported this view, and thought that there had been either temporary generalised damage to liver function or a more specific inhibition of gluconeogenesis. Peluffo et al. (1958) postulated that the hypoglycæmia might be due to rapid liberation of insulin as a result of rapid absorption of alcohol by fasting patients. We believe that poor nutrition is an important predisposing factor. The majority of the patients reported elsewhere, and those reported here, came from a low income level and were on poor diets. Three factors may have played a part in the production of hypoglycæmia in these patients: (1) a period of inadequate food intake; (2) increased utilisation of glycogen stores during the metabolism of alcohol; (3) decreased glycogen synthesis during the utilisation of these stores. The liver biopsy performed on 3 patients on admission demonstrated depletion of liver glycogen. This, in our view, had resulted from deficient intake of food and, more important, from a concomitant utilisation of carbohydrate during alcohol metabolism (Westerfield et al. 1943, Westerfield 1955, Westerfield and Schulman 1959). The quantity of alcohol consumed is thus likely to influence the ultimate amount of carbohydrate utilised. In health, however, only minor fluctuations in blood-sugar would be expected (Westerfield and Schulman 1959). Why then, in certain patients, should there be no adequate response to the glycogen depletion? We suggest that, in certain undernourished patients where ethyl alcohol has had a toxic action on the liver, failure of gluconeogenesis results from temporary dysfunction of the liver-cells produced by the toxic hepatitis. However, further investigation of the adrenal functions in undernourished persons is necessary.

One must still account for the dramatic and sustained therapeutic effect of small quantities of intravenous glucose. This took place even without intake of food during the succeeding twenty-four hours in 1 of our cases where the patient, mentally abnormal at the time, refused food: a similar finding has been reported by Bottura et al. (1949) and Neves et al. (1950). Probably, owing to the glycogen depletion and the hepatocellular dysfunction, there is an initial difficulty in response to the hypoglycæmic state, but, once the glycogen depletion has been corrected by glucose administration, and the stimulus (alcohol) for increased glycogen and carbohydrate utilisation has disappeared, the blood-sugar level is maintained. Peluffo et al. (1958) thought that administration of dextrose solution led to emergence from the hypoglycæmic coma through removal of excess insulin. But in 3 of our cases where liver biopsy was performed on admission, there was absence of glycogen; while, in a case where a patient with functional hyperinsulinism was admitted in coma to this hospital, an abundance of glycogen was present.

Whenever a patient is admitted in coma and has a history of imbibing alcohol, the possibility of postalcoholic hypoglycæmia should be considered. This is most important where patients are undernourished or are known chronic alcoholics. In many of the latter cases acute alcoholic intoxication is no doubt diagnosed, with disastrous results (Bottura et al. 1949). The history, however, is often obtained only after recovery, when dextrose solution has been administered. A smell of stale alcohol on the breath is sometimes helpful. Where no history is obtained, the varied manifestations of hypoglycæmia must be recognised. Bizarre neurological signs and abnormal mental states should always suggest the possibility of this diagnosis. Where hypoglycæmia is protracted, as in these cases, signs of adrenaline response are usually not present.

Once the diagnosis has been made the treatment is simple, and, where the period of hypoglycæmia has not been lengthy, the majority of patients recover without further complications. Early treatment, however, is essential, since otherwise death or permanent damage to the central nervous system may result (Conn and Seltzer 1955).

Summary

The clinical and biochemical findings in 23 cases of postalcoholic hypoglycæmia are described. A concomitant, mild, and transient toxic hepatitis was noted in all patients.

Ethyl alcohol was considered to be the toxin concerned. A long period of poor dietary intake was thought to have

resulted in the liver being especially vulnerable to toxins, such as ethyl alcohol.

We wish to thank Prof. J. Wainwright, Prof. E. B. Adams, Prof. H. Wallace, Dr. I. Robertson, Mr. C. Scholtz, Dr. J. Abramson, and Sister C. Majola for their help; Dr. S. Disler, superintendent of King Edward VIII Hospital, for permission to publish the cases; and Prof. F. Forman for advice.

REFERENCES

Bang, N. U., Iversen, K., Jagt, T., Madsen, S. (1958) *J. Amer. med. Ass.* **168,** 156.
Bottura, C., Neves, D. P., Mattar, E., De Oliveira, H. L., Ulhoa Cintra, A. B. (1949) *Rev. Hosp. Clin., S. Paulo,* **4,** 133.
Bowden, K. M., McCallum, N. E. W. (1949) *Med. J. Aust.* ii, 76.
Brown, T. McP., Harvey, A. M. (1941) *J. Amer. med. Ass.* **117,** 12.
Conn, J. W., Seltzer, H. S. (1955) *Amer. J. Med.* **19,** 460.
Hed, R. (1959) *Acta med. scand.* **165,** 161.
Hergt, K., Langin, J. L. (1957) *Amer. J. med. Sci.* **233,** 69.
Joubert, S. M., Hookins, K. W., Hunter, W. G. (1959) *S. Afr. J. Lab. clin. Med.* **5,** 1.
Karmen, A., Wroblewski, F., LaDue, J. S. (1956) *J. clin. Invest.* **34,** 126.
King, E. J., Wootton, I. D. P. (1956) Microanalysis in Medical Biochemistry, London.
Madsen, S., Bang, N., Iversen, K., Jagt, T. (1959) *Dan. med. Bull.* **6,** 33.
Neves, D. P., Faria, C. V., Furjoka, T. (1950) *Rev. Hosp. Clin., S. Paulo,* **5,** 115.
Peluffo, E., Scolpini, V., Grezzi, J., Tarallo, N. (1958) *Arch. Pediat. Urug.* **29,** 94.
Taylor, J. S. (1955) *Brit. med. J.* i, 648.
Tucker, H. St.G., Porter, W. B. (1942) *Amer. J. med. Sci.* **204,** 559.
Westerfield, W. (1955) *Tex. Rep. Biol. Med.* **13,** 559.
— Schulman, M. P. (1959) *J. Amer. med. Ass.* **170,** 197.
— Stotz, E., Berg, R. L. (1943) *J. biol. Chem.* **149,** 237.

SELECTIVE VAGOTOMY IN THE PREVENTION OF POST-VAGOTOMY DIARRHŒA

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IN the treatment of duodenal ulcer by vagotomy, diarrhœa is perhaps the most troublesome complication. Usually it is mild and patients do not seek advice for it; indeed, many are gratified at the alleviation of constipation. Even where it is severe it may be elicited only by questioning. In some patients, however, it is crippling and apparently permanent.

Lloyd Davies (1956), in his five-year review of the West London Hospital series, which had been collected from many centres, found diarrhœa in 22·5%. Burge and Pick (1958), in an eight-year review of the same series, found it in 30%. More recent studies at the West London Hospital have shown that after vagotomy and pyloroplasty it has sometimes persisted for ten years (Burge and Clark 1960).

The report of the National Committee on Peptic Ulcer of the American Gastroenterological Association (1952) does not discuss the severity of postoperative diarrhœa, but gives its prevalence at three years as 17·7%.

Grimson et al. (1947), describing the results of vagotomy in 57 patients with chronic duodenal ulceration, wrote: "Only four patients in this series have had persistent severe diarrhœa. Three of these have adequate gastroenterostomies." Grimson's figure, therefore, for severe persistent diarrhœa, was 5%. Clark in Aberdeen (1961) found diarrhœa in 22% of 67 patients. In 5% he classified it as severe.

The American Gastroenterological Association (1952) found that the incidence of diarrhœa was not related to the type of drainage procedure used, and this too has been the finding in the West London Hospital studies. Some have attributed the diarrhœa to gastric stasis resulting in decomposition of food, but gastric stasis is unusual when a drainage operation is added to vagotomy. Others have thought it of infective origin following gastric hypoacidity, but no clear evidence of an infective cause has been reported. In fact there is still no satisfactory explanation of persistent diarrhœa.

Many years ago at the West London Hospital it was noticed that in many patients who had had vagotomy the stools were always pale. Only one reference to this colour change has been found elsewhere—namely the remark of Grimson et al. (1947) that " some patients with diarrhœa (after vagotomy) state that the stools are lighter than normal in colour."

Scope and Aim of Investigation

Conflicting results have been obtained in experiments on the effects of vagal section on the liver and biliary system, on the pancreas, and on the small and large gut. The work of Pfeffer et al. (1952) in man, and of Pincus et al. (1948), suggests that pancreatic function may well be considerably impaired. Tanturi and Ivy (1938) showed that, in dogs, stimulation of the right vagus increased the volume of bile, and other workers have shown that insulin hypoglycæmia does the same (Bachrach 1954). But it seems fair to say that in man, according to present physiological opinion, the vagus nerves play no important part in hepatic or pancreatic function; and physiologists would probably not support the view that interruption of the vagal supply of any of these organs would lead to dysfunction causing symptoms. In recent years, however, we have learnt that the hormonal phase of gastric acid formation is not an independent thing but is diminished when the acid-secreting cells lose their nerve-supply after vagal section. Perhaps the hormonal control of other organs is also impaired when their vagal innervation is lost.

Reports on the effect of vagal section on the motility of the small gut and colon have likewise been conflicting (Cannon 1906, Collins et al. 1948).

It has been known since 1948 (Franksson 1948, Jackson 1948) that the hepatic branch of the anterior vagus and the cœliac division of the posterior could be preserved during gastric vagotomy in man. The hepatic branch, or branches, of the anterior vagus supplies the liver, the biliary apparatus, the gastric antral region, the pylorus, and the duodenum. Possibly it has a wider area of innervation than this. The cœliac division of the posterior nerve enters the cœliac ganglion. Although its fibres have never been traced through the ganglion, presumably it supplies the pancreas and the intestinal tract.

At the West London Hospital an attempt was made to find what place, if any, preservation of one or both of these branches might have in the prevention of diarrhœa and of pale motions after vagotomy (Burge 1960). Of the three operations compared, type 1 is of course the standard procedure, and obviously denervates all the abdominal organs. The other two are modifications:

Type 1.—Total abdominal vagotomy (fig. 1).

Type 2.—Complete anterior vagal section with preservation of the cœliac division of the posterior nerve (fig. 2).

Type 3.—Preservation of the hepatic branch of the anterior nerve and the cœliac division of the posterior nerve (fig. 3).

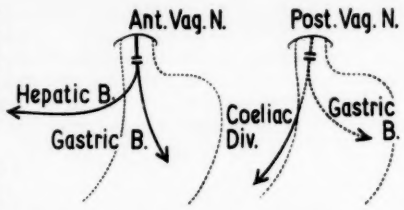


Fig. 1—Total abdominal vagotomy, type 1.

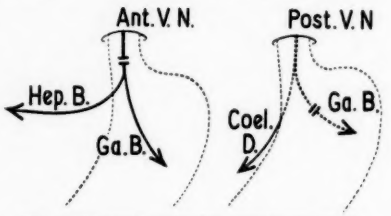


Fig. 2—Posterior selective vagotomy, type 2.

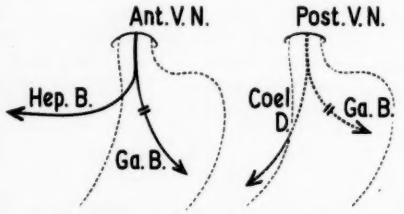


Fig. 3—Bilateral selective vagotomy, type 3.

All were combined with a short-loop posterior gastrojejunostomy.

This inquiry suggested (fig. 4) that selective vagotomy might help to prevent diarrhœa, and that the type-3 operation was better for this purpose than the type 2. We now report a much bigger study undertaken partly at the West London Hospital and partly at the Glasgow Royal Infirmary.

Findings

In Glasgow, where some severe cases of post-vagotomy diarrhœa had been recognised, it was first necessary to determine what proportion of patients had a change in bowel habit after the standard type-1 operation. An investigation was also made into the effect of gastrojejunostomy alone.

To assess diarrhœa in these two preliminary series of Glasgow patients, a postal questionnaire was used, patients being asked to indicate whether their bowel habit had changed since operation, and also specifically whether they had had diarrhœa or noticed a change in colour of the motion. Those who replied in the affirmative were interviewed and their diarrhœa was assessed as:

1. *Slight.*—Mild sporadic attacks only.
2. *Moderate.*—Sporadic or persistent attacks, with either urgency or distress but not both.
3. *Severe.*—Sporadic or persistent attacks with both urgency and distress.

Since patients often have diarrhœa in the early postoperative period, no assessments were made under three months. If the symptom does not clear up by that time it seems likely to persist.

This inquiry showed that in Glasgow the incidence of post-vagotomy diarrhœa (30%) was roughly the same as had been found in London (26%).

It was then agreed that the two hospitals would together complete and study the results of 100 cases of each of the three types of operation, all combined with posterior gastrojejunostomy.

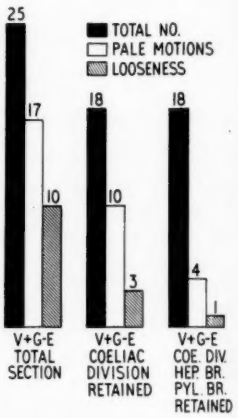


Fig. 4—Incidence of post-vagotomy diarrhœa.

Diarrhœa

When the type-2 series (preservation of the cœliac division of the posterior nerve) reached 73 cases, it seemed clear that preservation of the cœliac division alone did not influence the incidence or severity of the diarrhœa, and this series was therefore carried no further.

Fig. 5 shows that with the type-3 procedure (preservation both of the cœliac division of the posterior nerve and of the hepatic branch of the anterior nerve) fewer patients had diarrhœa and there were no severe cases. No difference is apparent between types 1 and 2.

Of 84 cases treated at least ten years previously by gastroenterostomy without vagotomy, only 2 had mild diarrhœa possibly dating from the operation. Persistent diarrhœa therefore is not a complication of gastroenterostomy alone.

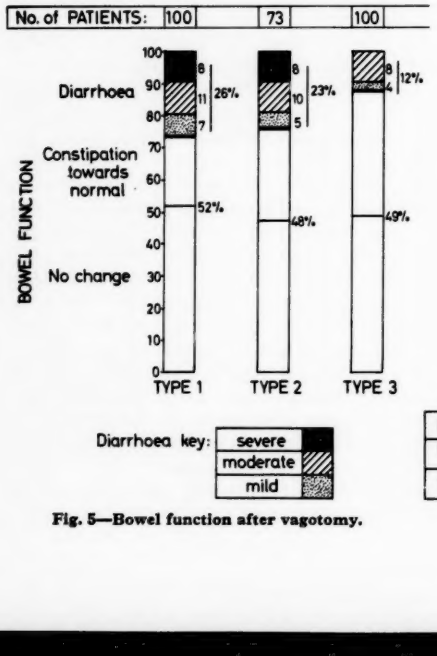
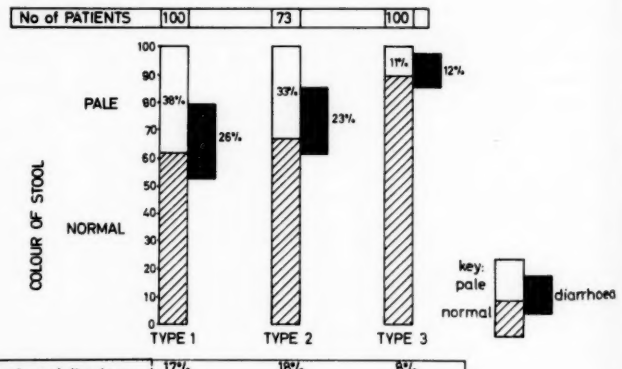


Fig. 5—Bowel function after vagotomy.



	TYPE 1	TYPE 2	TYPE 3
Pale stools and diarrhoea:	17%	18%	8%
Pale stools without diarrhoea:	21%	15%	3%
TOTAL of PALE STOOLS:	38%	33%	11%

Fig. 6—Pale stools after vagotomy, and relation to diarrhœa.

Pale Stools

Fig. 6 shows that the proportion of patients having pale stools after operation was also much lower with the type-3 operation. While colour change was not necessarily associated with diarrhœa, 70% of patients having diarrhœa also had pale stools.

Discussion

The evidence presented depends to some extent on patients' own assessment of their postoperative symptoms—particularly as regards the severity of the diarrhœa. But each patient who had undergone selective vagotomy was interviewed by two independent observers, neither of whom was concerned in the treatment, and these observers very seldom differed over the category appropriate to any patient.

Our investigation suggests that preservation of the cœliac branch of the posterior vagus nerve does not prevent diarrhœa or pale stools. But when the hepatic branch of the anterior vagus nerve was also preserved, there was far less interference with normal function. Preservation of this branch alone might be equally effective, and this is being investigated.

We should point out that pale stools and diarrhœa may not be related; for the one can occur without the other. We should also make it clear that the anatomy of the anterior vagus and its branches is sometimes complex. Swan (1830), in describing this branch, showed it in his beautiful diagrams as a plexus. In 1 patient we have found as many as four anterior nerve-trunks, each giving hepatic branches. Those of us who have performed the operations now believe that in many cases we have preserved only part of the plexus, though complete preservation should nearly always be possible. Incompleteness of preservation probably accounts for the 12% of diarrhœa and the 11% of pale motions found even with the type-3 operation.

Assessment at three months was chosen because of the temporary diarrhœa, sometimes seen after operation, which we attribute to traction of the retained nerve by thread " stays "—in much the same way as branches of the facial nerve can undergo temporary paresis during parotid dissection.

We hope later to publish results of a further series in which the cœliac division is completely divided and the hepatic plexus of the anterior nerve is completely retained. The early work on this series seems to confirm our present findings.

Summary

An earlier study at the West London suggested that the diarrhœa and pale stools often following vagotomy could be prevented by preserving the hepatic plexus of the anterior vagus and the cœliac division of the posterior vagus.

Investigation of a larger number of cases, at the West London Hospital and the Glasgow Royal Infirmary, indicates that preservation of the hepatic branches (or plexus) of the anterior vagus is important, but that preservation of the cœliac division of the posterior nerve makes little or no difference.

For preservation of the hepatic plexus full knowledge of its formation from the anterior vagal trunks is required.

A further series is being studied in which the cœliac division of the posterior nerve is divided and the hepatic plexus of the anterior nerve is preserved. So far, the results support our previous findings.

We should like to thank the Dan Mason Research Foundation of the West London Hospital Medical School for all the help they have given us in connection with this work.

We should also like to thank the nursing and theatre staff at the West London Hospital and at Glasgow Royal Infirmary for all their help; and, in particular, Sister Whelan for the very great interest she has shown and the trouble she has taken since this work first began at the West London Hospital.

REFERENCES

Bachrach, W. H. (1954) *Physiol. Rev.* **34**, 566.
Burge, H. (1960) *Ann. R. Coll. Surg. Engl.* 1960, **26**, 231.
— Clark, P. A. (1960) *Gastroenterology*, **39**, 572.
— Pick, E. J. (1958) *Brit. med. J.* i, 613.
Cannon, W. B. (1906) *Science*, **24**, 764.
Clark, C. G. (1961) *Brit. med. J.* i, 1250.
Collins, E. N., Crile, G., Jr., Davis, J. B. (1948) *Gastroenterology*, **11**, 453.
Committee on Surgical Procedures (1952) *ibid.* **22**, 3.
Davies, J. A. L. (1956) *Brit. med. J.* ii, 1086.
Franksson, C. (1948) *Acta. chir. scand.* **96**, 409.
Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H., Rundles, R. W. (1947) *J. Amer. med. Ass.* **134**, 925.
Jackson, R. G. (1948) *Arch. Surg., Chicago*, **57**, 333.
Pfeffer, R. B., Stephenson, H. E., Jr., Hinton, J. W. (1952) *Ann. Surg.* **136**, 585.
Pincus, I. J., Thomas, J. E., Lachman, P. O. (1948) *Fed. Proc.* **7**, 94.
Swan, J. (1830) A Demonstration of the Nerves of the Human Body; plates III-VII.
Tanturi, C. A., Ivy, A. C. (1938) *Amer. J. Physiol.* **121**, 270.

THE HEPATIC VAGAL PLEXUS

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IN 1830 Swan gave a series of lectures to the Royal College of Surgeons of England on the nerves of the human body. His book (Swan 1830), which illustrates his work in detail, shows the anterior vagus nerve emerging beneath the diaphragm in several trunks, and what is usually called the hepatic branch of the anterior vagus he draws and describes as the " hepatic plexus ".

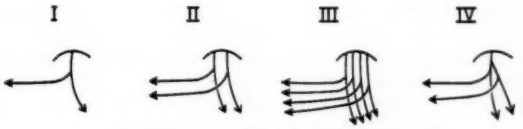

Fig. 1—The anterior hepatic plexus.

In performing anterior selective vagotomy I have carefully noted variations in the anterior vagus and its branches. At operation it is possible to demonstrate the hepatic branches as they come off the main trunks, and my observations have shown me that in previous operations I must sometimes have unwittingly severed some of the branches I was trying to save.

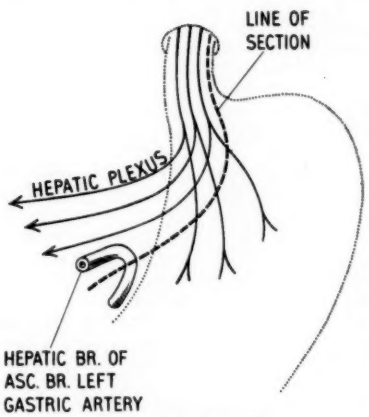

Fig. 2—Line of section.

So far I have seen the anatomical patterns shown in fig. 1, and almost certainly there are others. Until recently I thought that when there was more than one trunk, the hepatic branch or branches arose from the trunk placed furthest to the right; but it now seems that

when the anterior vagus exists as two or more trunks, each of these may supply a branch or branches to the hepatic plexus. When a single anterior trunk divides beneath the diaphragm, each of its branches may supply the plexus.

With knowledge of these variations, it is not difficult to preserve the entire plexus—as I have done in a patient with four anterior nerve-trunks. Each trunk should be carefully identified, and in performing anterior selective vagotomy, the line of section should be kept low—below the point at which a hepatic branch may arise from the furthest left vagal trunk or gastric branch (fig. 2).

During this operation it is helpful to hold up the nerve-trunk or trunks with thread " stays "; but, when this is done, traction on the nerves may lead to a temporary paresis, and diarrhœa. A better plan, therefore, is to insert a short piece of very fine rubber tubing between the nerve-trunks and the œsophageal wall.

REFERENCE

Swan, J. (1830) A Demonstration of the Nerves of the Human Body; plates III–VII. London.

TRETAMINE COMPARED WITH NITROGEN MUSTARD IN THE PALLIATION OF INOPERABLE LUNG CANCER

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NITROGEN mustard (methyl bis [β-chloroethyl] amine) has been used for many years in the palliation of lung cancer. Last year Jack et al. (1960) reported striking results with another cytotoxic agent—tretamine (2 : 4 : 6-triethyleneimino-S-triazine, triethylene melamine [T.E.M.]), and recommended trial of a single 20–30 mg. intravenous dose for the treatment of inoperable cases. It was therefore decided to compare the results of tretamine therapy with those of nitrogen mustard.

Method

Patients with proved inoperable bronchial carcinoma who had dyspnœa, dysphagia, or the syndrome of mediastinal compression were allocated at random to tretamine or nitrogen-mustard treatment. Chest radiography was carried out, and the severity of symptoms was assessed just before treatment was started and weekly for four weeks thereafter. White-blood-cell counts were performed just before the start of treatment, and then at least twice a week for four weeks thereafter; platelet-counts were done when indicated.

Tretamine or nitrogen mustard was given in a single intravenous dose. To minimise the nausea and vomiting which may follow administration of these agents, the regimen advocated by Bass (1960) was employed: the drug was given in the evening, and two hours before its administration sodium amylobarbitone gr. 3 was given, and this was repeated an hour before and again at the time of administration. If the patient awoke during the night a further gr. 3 was given.

18 patients received tretamine. The dose was at first 25 mg., but this was later reduced to 20 mg. and then to 15 mg. The dosages for the 18 patients (mg. per kg. body-weight) were 0·3, 0·34, 0·35, 0·4, 0·4, 0·4, 0·4, 0·4, 0·4, 0·4, 0·4, 0·4, 0·46, 0·46, 0·5, 0·5, 0·5, 0·66. 16 patients received nitrogen mustard. The dose was at first 30 mg. per kg. body-weight, but this was later increased to 40 mg. per kg. The dosages for these patients (mg. per kg. body-weight) were: 0·3, 0·35, 0·4, 0·4, 0·5, 0·5, 0·5, 0·6, 0·6, 0·6, 0·6, 0·66, 0·7, 0·7, 0·8, 0·8.

Results

4 patients in the tretamine series died, but since they survived until the third week after receiving the drug the results in all 18 cases were suitable for analysis. 1 extremely ill patient in the nitrogen-mustard series died two days after receiving the drug; thus the results in only 15 of the 16 nitrogen-mustard cases were suitable for analysis.

TABLE I—SYMPTOMATIC RELIEF

Agent	Extent of relief				Total
	Pronounced	Moderate	Slight	None	
Tretamine ..	7	3	4	4	18
Nitrogen mustard ..	11	2	1	1	15

Symptomatic Relief

Symptomatic relief was classified as pronounced, moderate, slight, or none. The results are shown in table I. 10 (55%) of the tretamine patients obtained substantial relief (pronounced or moderate) compared with 13 (86%) of the 15 patients in the nitrogen-mustard series. Symptomatic improvement, when it occurred, began within a week of drug administration.

Radiological Response

Improvement in the radiological appearances in chest films was also classified as pronounced, moderate, slight, or none. The results are shown in table II. Substantial (pronounced or moderate) radiological improvement occurred in 7 (39%) of the 18 tretamine cases and in 9 (60%) of the nitrogen-mustard cases. In cases in which radiological improvement occurred, it was usually maximal by the end of the third week, though in some cases further improvement occurred in the fourth week.

TABLE II—RADIOLOGICAL IMPROVEMENT

Agent	Extent of relief				Total
	Pronounced	Moderate	Slight	None	
Tretamine ..	4	3	3	8	18
Nitrogen mustard ..	7	2	2	4	15

Early Side-effects

The severity of nausea or vomiting in the period immediately after drug administration was assessed. Of the 18 tretamine cases side-effects were pronounced in 5, moderate in 8, mild in 4, and absent in 1. Of the 15 nitrogen-mustard cases side-effects were pronounced in 1, moderate in 6, mild in 4, and absent in 4.

Late Side-effects

In 3 of the 18 tretamine cases there was no significant reduction in the white-blood-cell count. In the other 15 cases a reduction was noted in the first week, and by the second week the count in 12 cases had fallen to less than 1000 per c.mm. In these 12 cases the platelet-count was also greatly reduced. 14 of the tretamine patients developed hæmorrhagic lesions of some sort. 12 had skin petechiæ, and in 6 of these cases this was accompanied by bleeding from some other part of the body. In 2 further cases there was hæmorrhage unassociated with skin involvement—in 1 case from the nose, and in the other from the gums. Petechiæ first appeared between the eleventh and sixteenth day after drug administration, most commonly on the twelfth or thirteenth day. Usually petechiæ stopped appearing after five or six days, although in 1 case they continued to appear over a period of fourteen days. In 1 case there was ulceration of the gums. Side-effects were severe in 8 cases. Despite supportive treatment with antibiotics, prednisolone, and blood-transfusion, 4 patients died (on the seventeenth, nine-

teenth, twenty-first, and twenty-third days after treatment), and although their condition was already poor they would have survived longer but for the drug side-effects. The dosage in these cases was 0·5, 0·46, 0·4, and 0·3 mg. per kg. body-weight. The patient with 0·3 mg. per kg. had widespread petechial hæmorrhages, and died as a result of bleeding from a gastric carcinoma which was found at necropsy to coexist with bronchial carcinoma. The patient with the highest dosage in the series—0·66 mg. per kg.—had no serious side-effects although the white-blood-cell count fell to less than 1000 per c.mm. in the third week, and a few skin petechiæ developed.

In only 1 of the 15 patients in the nitrogen-mustard series did the white-blood-cell count fall below 2500 per c.mm.; in that case (dose 0·8 mg. per kg.) the count was as low as 800 per c.mm. on the tenth day after drug administration, but rapidly rose again. No overt side-effects occurred in any of the nitrogen-mustard cases.

Discussion

The results of the present investigation do not support the suggestion of Jack et al. (1960) that tretamine therapy is likely to prove an advance in the management of inoperable lung cancer. It produced gratifying symptomatic relief and impressive radiological improvement in some cases, but on the whole nitrogen mustard proved more effective. Moreover, in a high proportion of cases the benefits of tretamine were bought at the expense of unpleasant and dangerous side-effects due to the toxic action of the drug on the hæmopoietic tissues, whereas this complication was not found in any of the cases treated with nitrogen mustard.

Anaplastic carcinoma is reported to respond better than other types to nitrogen mustard (Kent and Reh 1950, Lynch et al. 1950, Levine and Weisberger 1955, Bass 1960) and the position with tretamine is probably similar. It is therefore worth mentioning that 66% (12 out of 18) of the neoplasms in the tretamine series were anaplastic, compared with 60% (9 out of 15) in the nitrogen-mustard series.

With experience the dose of tretamine was cut: the lowest dose was 0·3 mg. per kg. body-weight, but even at this level fatal hæmorrhage from a malignant ulcer occurred. Lower dosage levels would, therefore, be required to avoid hazardous side-effects; but this would presumably reduce the clinical effectiveness of the drug, already less than that of nitrogen mustard at the dosage used in this trial. It is well known that nitrogen-mustard therapy, though often extremely valuable for the relief of distressing symptoms in inoperable lung cancer, only temporarily arrests the advance of the disease. The results of a four-to-eighteen-month follow-up of the patients in the present trial are in keeping with this experience, and indicate also that any check to the malignant process brought about by tretamine is no more lasting: in all cases in which improvement resulted from treatment with either drug, deterioration ensued—occasionally even within a month. The evidence of this investigation, therefore, strongly suggests that tretamine has no advantages over nitrogen mustard in the management of inoperable lung cancer and is much more dangerous.

Summary

Patients with symptoms due to inoperable lung cancer were allocated at random to treatment with tretamine or nitrogen mustard. They were given a single intravenous dose of 15 to 25 mg. tretamine or 30 to 40 mg. nitrogen mustard.

Of 18 tretamine-treated patients, 10 (55%) obtained substantial symptomatic relief and 7 (39%) showed substantial radiological improvement. Of 15 nitrogen mustard treated patients, 13 (86%) obtained substantial symptomatic relief and 9 (60%) showed substantial radiological improvement.

Of the 18 tretamine-treated patients 14 had side-effects resulting from the toxic effect of the drug on the hæmopoietic tissues, and in 8 instances these were serious. None of the 15 patients treated with nitrogen mustard had such side-effects.

Tretamine proved to be less effective and much more dangerous than nitrogen mustard in the palliation of inoperable lung cancer.

REFERENCES

Bass, B. H. (1960) *Brit. med. J.* i, 617.
Jack, G. D., Doyle, L., Palejwalla, M. M. (1960) *Lancet*, i, 206.
Kent, L., Reh, E. P. (1950) *Dis. Chest*, **17**, 190.
Levine, B., Weisberger, A. S. (1955) *Ann. intern. Med.* **42**, 1089.
Lynch, J. P., Ware, P. F., Gainsler, E. A. (1950) *Surgery*, **27**, 368.

TWO CASES OF PHÆOCHROMOCYTOMA IN ONE PRACTICE IN ONE YEAR

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THE first description of the clinical syndrome of paroxysmal hypertension, sweating, headaches, and pallor produced by a phæochromocytoma was by Fraenkel in 1886, and the first tumour was removed successfully, with complete reversal of hypertension, by C. H. Mayo in 1927. The condition was thought to be rare, and up to 1952 Symington and Goodall (1953) collected 283 cases (67% of which were demonstrated post mortem) from published reports. Graham (1951) found an incidence of 1 in 200 of all hypertensives selected for sympathectomy. Many more cases have been reported recently because of better techniques of diagnosis, and greater awareness of the condition.

Two cases have been detected in the past year in my practice of about 2800 patients, and the purpose of this report is to show that these tumours may be even more common than is now supposed. The two cases also show how differently the tumours may present clinically, and how their presentation may differ from the classical syndrome.

Case-reports

THE FIRST CASE

A man of 55 first complained, in 1953, of a bout of "fullness" in the head and of excessive perspiration at mealtimes. He had periods of feeling "weak and listless" for several days. His blood-pressure at this time was recorded as 170/90 mm. Hg.

During 1956 he complained of attacks of nausea with abdominal distension, dizziness, with a constricted feeling in the head. His wife said his pulse was slow during an attack, his face became pale, and he perspired profusely. These attacks came on about every 6 weeks, they lasted about 12 hours, and they were always followed by listlessness for several days. Readings of his blood-pressure during an attack were as high as 190/120. When referred for a second opinion in January, 1957, he was thought to have a labile hypertension which was aggravated by considerable domestic stress. In 1958 he had two attacks of throbbing occipital headache followed by vomiting; he did not seek advice because he thought he was suffering from migraine. His blood-pressure was not recorded.

From July, 1959, the occipital headaches with vomiting became more severe and were often followed by listlessness.

He continued to work until October, when his blood-pressure was recorded as 210/115 although his fundi were normal. He was first seen in one of these attacks, with projectile vomiting, severe headache, pallor, profuse perspiration, a bradycardia of 60 per minute, and a blood-pressure of 230/130. The attack lasted about 12 hours. When he was admitted to hospital, under Dr. W. M. Priest, several days later, a phæochromocytoma was suspected.

Investigations

Urinary catecholamine excretion was greater than 1000 μg. per 24 hours (by the method of Hingerty 1957). Biological assay showed a noradrenaline excretion of 1020 μg. per 24 hours. The intravenous phentolamine test was positive. Perirenal air insufflation suggested a tumour on the right.

Operation

The right adrenal was explored by Mr. Geoffrey Taylor in November, and a tumour 2 cm. in diameter was removed. The patient's recovery was uneventful. Now, 2 years later, he is free from all symptoms, and his average blood-pressure remains at 160/90.

THE SECOND CASE

A man of 51 first complained to his doctor in 1952 of general weakness and debility, with bouts of pulsation in his chest and sweating. His blood-pressure was 150/90, and the resting pulse-rate 80 per minute. He was reassured and did not attend again until 4 years later, when he complained of " spasms " of perspiration and palpitations. His blood-pressure was 190/108. His facial colour had been very high for 3 years, and he could never sit for long in a heated room because of excessive sweating.

In 1957, when his doctor saw him at home, he complained of excessive palpitation, perspiration, and general weakness. His blood-pressure was 200/128. He was kept in bed for 3 weeks, and he was then referred to hospital for investigation and treatment of his hypertension. He was thought to have a labile hypertension of chiefly emotional basis, and he was reassured. At this time he was having several attacks of sweating and palpitation each week.

He kept away from doctors until July, 1958, when he came to me complaining of " a feeling of nervous tension ". His blood-pressure was 200/125. I asked him to return for further investigation, and he did so exactly a year later; his blood-pressure was then 200/95, and he had normal fundi.

I did not see him again until July, 1960, when he had giant urticaria which persisted for 2 weeks. Meanwhile, he became more and more agitated, and I was eventually called to see him in bed with an attack of sweating, palpitation, and extreme weakness. His wife said that this was identical with the attack he had had in 1957. It started with abdominal discomfort and a pounding sensation working slowly up from his abdomen to his chest; he was sweating excessively but his feet felt very cold, and during this period he passed urine every half-hour. When I saw him his face was mauve but he was not dyspnœic. He was sweating so much that he was saturating the bed. His hands and face were warm, but his feet were cold, with blotchy cyanosis. His peripheral pulses were present. His pulse-rate was 140 per minute, blood-pressure 180/150, with a pulse-pressure of 30 mm. Hg and temperature 99°F. He was mentally alert. I felt a swelling in the right side of the abdomen.

Because of the previous case, and particularly because of the hypertension and excessive sweating, I thought he might have a phæochromocytoma. He was seen by Dr. Stephen Whittaker, and admitted to Warwick Hospital.

Investigations

Urinary catecholamine excretion was greater than 1000 μg. per 24 hours. The intravenous phentolamine test was positive. Urinary excretion of 3-methoxy-4-hydroxymandelic acid was greatly increased (by the method of Gitlow et al. 1960). An intravenous pyelogram showed that the calyces of the right kidney were distorted.

Operation

A large benign phæochromocytoma 12 cm. in diameter, and weighing 900 g., was removed with some difficulty from the pole of the right kidney by Mr. Taylor. The postoperative phase was stormy, with a period of anuria; but he recovered, and he is now back at work, with a blood-pressure of 130/80 and a blood-urea of 68 mg. per 100 ml. His high facial colour has completely disappeared.

Discussion

Although these two cases presented differently they had several features in common. One was the length of history. The first case had symptoms for 7 years, and the second for 12 years, which illustrates the benign course of the illness; neither tumour was in fact malignant. The patients seem to have fairly resilient vascular systems because they have as yet shown no permanent damage. Both tumours were on the right side, as in about 80% of all reported cases. The second patient had by far the larger tumour, and it could be felt on abdominal examination.

Estimation of the pressor amines in the urine has helped to make the diagnosis easier in recent years; but Litchfield and Peart (1956) have reported a case in which these substances were within normal limits even during an attack, and they emphasise the importance of basing the diagnosis on clinical signs and symptoms.

I was able to see both patients in attacks. The only common factor was sweating. The second case had marked tachycardia, but the first had bradycardia. Freedman et al. (1958), describing five cases associated with diabetes, suggested that those tumours that secrete mainly adrenaline may cause metabolic upsets, including frank diabetes or occasionally a raised basal metabolic rate with enlargement of the thyroid gland. Because the second patient had lost much weight over the past 2–3 years, his tumour probably excreted an excessive amount of adrenaline. The first patient showed no loss of weight; his symptoms followed the more classical lines, with normal blood-pressure between attacks and paroxysms after emotional upsets. He twice precipitated an attack by practising Yogi which involved standing on his head for some minutes. He always had bradycardia during his attacks, and the main features were projectile vomiting with severe occipital headaches. His tumour probably secreted predominantly noradrenaline, thus accounting for the bradycardia. The second case had a sustained hypertension between attacks; Helps et al. (1955) think that the majority of cases present in this manner.

Finally, I estimated the number of known hypertensives in my practice, using the criteria of random diastolic pressures of 110 mm. Hg and over for patients below the age of 60, and 120 mm. Hg and over for older patients. The readings were taken either sitting or standing. There were nine hypertensive men and seven women under 60, and eleven men and thirty-six women over 60. Many of these were reassessed with the possibility of phæochromocytoma in mind. The 3-methoxy-4-hydroxymandelic-acid–excretion test and Hingerty screening test were used when the signs and symptoms included labile hypertension with bouts of tachycardia or " pulsation in the chest " and sweating. The menopausal female may be a problem; but pallor is generally absent during the " hot flush ", and usually present in attacks due to phæochromocytoma. The second case, however, showed marked flushing of the face and neck during attacks, and his wife remarked on the similarity of his symptoms with those of her own menopause.

Phæochromocytoma is probably not as rare a tumour as has been thought; and, if the general practitioner keeps

the condition in mind, he has a better chance of spotting an early case than a consultant has because he tends to see far more cases of labile hypertension. Both my cases at one stage or other were particularly shy of doctors, and I have learnt to pay more attention to the evidence of wives and relatives.

Summary

Two cases of phæochromocytoma were found in a medium-sized general practice in 1 year. They presented in different ways, though they both had attacks of sweating, and hypertension was found.

I should like to thank Dr. Stephen Whittaker for his help and encouragement in the preparation of this paper; Dr. W. M. Priest for allowing me to report the first case; and also Dr. A. P. Prior and Mr. T. P. Whitehead, F.R.I.C., of the Central Pathological Laboratory, Warwick, for their help and patience.

REFERENCES

Fraenkel, F. (1886) *Virchows Arch.* **103**, 244.
Freedman, P., Moulton, R., Rosenheim, M. L., Spencer, A. G., Willoughby, D. A. (1958) *Quart. J. Med.* **27**, 307.
Gitlow, S. E., Urnstein, L., Mendsowitz, M., Khassis, S., Kruk, E. (1960) *Amer. J. Med.* **28**, 921.
Graham, J. B. (1951) *Surg. Gynec. Obstet.* **92**, 105.
Helps, F. P. W., Robinson, K., Ross, E. J. (1955) *Lancet*, ii, 267.
Hingerty, D. (1957) *ibid.* i, 766.
Litchfield, J. W., Peart, W. S. (1956) *ibid.* ii, 1283.
Symington, T., Goodall, A. L. (1953) *Glasg. med. J.* **34**, 75.

DEATH FROM PHÆOCHROMOCYTOMA

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AN apparently healthy patient died recently after anæsthesia for a simple operation, and the cause of death was found at necropsy to be a phæochromocytoma. Another death after operation in the presence of an undisclosed phæochromocytoma has previously been reported from this group of hospitals (Harrison and Seward 1954).

Case-report

The patient was a cheerful thin unmarried schoolteacher, aged 44—the headmistress of an infants' school. She was admitted to hospital in High Wycombe on March 8, 1961, for removal of a small mass (present for two weeks) in the left breast. She gave no history of previous operations, but seventeen months before she had sought advice for pain and swelling of one ankle, and at that time her blood-pressure was 120/80 mm. Hg. She suffered from attacks of migrainous headache, for which she took ergotamine tartrate. Clinical examination before the operation revealed nothing abnormal except the swelling in the breast; her blood-pressure was 120/70.

Operation

On the morning of operation the blood-pressure was 125/70. Premedication was with papaveretum 20 mg. and scopolamine 0·44 mg. Anæsthesia was induced an hour later with thiopentone 400 mg. and suxamethonium 70 mg. and it was maintained with endotracheal nitrous oxide, oxygen, and halothane at a concentration 2% falling to ½%, from a 'Fluotec' apparatus. Anæsthesia was uneventful. The pulse-rate was 80 per minute, and no change in rhythm was noticed by digital palpation; the blood-pressure was not recorded during the operation. The mass in the breast was found to be cystic and benign, and the operation was soon over. At the end the patient was pale, the pulse-rate was 80 per minute, anæsthesia was light, and she was considered fit to return to the ward. She was in the operation suite, which has no recovery room, for about thirty-five minutes.

Fifteen minutes later I was summoned to the ward because the patient was restless and cyanosed, and had a very rapid pulse. Because I was anæsthetising the next case, I could not see her for another ten minutes or so. She was then collapsed, pale, and sweating, with gasping respiration, dilated pupils, a faint and irregular pulse of more than 140 per minute, and frothy sputum in the mouth and pharynx, which were barely being kept clear by suction. The blood-pressure was difficult to measure but was less than 100 mm. Hg. Tracheobronchial toilet was carried out. She was given hydrocortisone 100 mg. intravenously because it seemed possible that she might have had steroid therapy while working away from home and not revealed it. Her condition deteriorated rapidly. She was given oxygen, artificial respiration, intracardiac nikethamide, and external cardiac massage, but she died about ninety minutes after the induction of anæsthesia.

Necropsy Findings

Both lungs showed extreme generalised œdema, with congestion. The entire bronchial tree was filled with frothy hæmorrhagic fluid. There was no hint of inflammation, inhalation of vomit, or pulmonary embolism. Both lower lobes and both upper lobes posteriorly were partly collapsed. The appearances were those found in acute left ventricular failure, and both chambers of the right side of the heart were slightly dilated.

The left adrenal gland was normal in size, but thinner than normal on section. The right adrenal gland was enlarged by a tumour of the medulla 4 cm. in diameter. Section of the tumour showed clumps of irregular cells split by fine bands of fibrous tissue, with some attempted tubule formation in places.

Discussion

Phæochromocytoma is a rare but well-documented tumour. Experience has shown that patients with an unsuspected phæochromocytoma who undergo operation for some other condition are very poor risks. A number of deaths have been reported (Apgar and Papper 1951, Crowther 1951, Swan 1951, Koonce et al. 1952, Harrison and Seward 1954, Henry 1954, Steen 1957, Coates and Rigal 1961).

In Coates and Rigal's case (1961) hypertension was not observed, though other manifestations of an "attack" were obvious—i.e., dyspnœa, tachycardia, peripheral vasoconstriction, and pupillary dilatation. Their patient had been taking ergotamine tartrate for migraine, and they suggested that this might act as an anti-adrenaline substance. The patient whose death is reported above had also been taking ergotamine for migraine; she also showed dyspnœa, tachycardia, peripheral vasoconstriction, and pupillary dilatation. No increase of blood-pressure was recorded, though monitoring was not complete and a transient rise could have escaped notice.

Death due to unsuspected phæochromocytoma may follow a simple short operation. The risk is probably less if the operation is severe and lengthy, because the monitoring is more thorough and there is time for the tumour to reveal itself while observation is close. Ainley-Walker and Woodward (1959) reported the case of a patient undergoing dorsal laminectomy, who began to bleed excessively, and whose pulse became irregular and fast; phæochromocytoma was suspected, appropriate action was taken, the diagnosis was confirmed by finding catecholamines in the urine, and the tumour was removed at a later date. With thorough monitoring of every case, perhaps this triumph of anæsthetic management could be repeated.

It would be valuable to know how many people with an undisclosed phæochromocytoma are at risk. Graham (1951) estimated that in the United States there should be 600–800 new cases per year; and, if the incidence is the same, this would suggest about 200 new cases per

year in Britain. Ainley-Walker and Woodward (1959) point out that, with two million anæsthetics being given each year, about 1 in 25 of the population receives an anæsthetic; therefore 8 people with phæochromocytomas may be given anæsthetics every year. The High Wycombe group of hospitals serves a population of 142,000, and about 6000 operations are performed in hospital every year. During ten years—and 60,000 operations—two deaths have followed surgery in patients with undisclosed phæochromocytomas. In this period no other cases of phæochromocytoma have been discovered, though search is always made where indicated.

Summary

A 44-year-old woman died after the surgical removal, under general anæsthesia, of a benign mass in the breast. A phæochromocytoma of the adrenal gland was found at necropsy.

The patient's symptoms were dyspnœa, tachycardia, peripheral vasoconstriction, and pupillary dilatation. There was no apparent rise in blood-pressure above 125/70 mm. Hg. She had been taking ergotamine tartrate for migraine.

Two deaths from undisclosed phæochromocytoma have been reported after operation (in ten years) in a hospital group serving a population of 142,000, and with 6000 operations per year.

I should like to thank Mr. R. A. K. Wiener for permission to publish this case-report, and Dr. H. J. Harris for the necropsy report.

REFERENCES

Ainley-Walker, J. C. S., Woodward, J. W. (1959) *Brit. J. Anæsth.* **31**, 167.
Apgar, V., Papper, E. M. (1951) *Arch. Surg., Chicago*, **62**, 634.
Coates, P. A., Rigal, W. M. (1961) *Lancet*, i, 1374.
Crowther, K. V. (1951) *Brit. med. J.* i, 445.
Graham, J. B. (1951) *Int. Abstr. Surg.* **92**, 105.
Harrison, B. L., Seward, E. H. (1954) *Brit. med. J.* ii, 1077.
Henry, M. U. (1954) *ibid.* p. 344.
Koonce, D. H., Pollock, B. E., Glassy, F. J. (1952) *Amer. Heart J.* **44**, 901.
Steen, T. R. (1957) *Anæsthesia*, 12, 80.
Swan. H. J. C. (1951) *Brit. med. J.* i, 440.

PAROXYSMAL HYPOTENSION DUE TO AN ADRENALINE-SECRETING PHÆOCHROMOCYTOMA

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IN the case described here the patient had recurrent episodes of hypotension associated with other unusual clinical features. The syndrome was found to be due to a phæochromocytoma.

Case-report

In 1944, the patient, a girl aged 18, underwent thyroidectomy on account of thyrotoxicosis associated with a goitre causing tracheal compression. Subsequently she was well until 1954 when she began to have attacks of high epigastric pain associated with some tightness in the chest. At the outpatient department of the Royal Infirmary, Edinburgh, she was shown by barium-meal examination to have a duodenal ulcer. She was seen again as an outpatient in 1955 owing to persistence of her symptoms; the pain was now mainly in the right hypochondrium and tended to radiate through to the back. In January, 1956, the patient was admitted to hospital, where she received an ulcer regimen and became free of symptoms. In October of the same year she was readmitted on account of a very acute exacerbation of " ulcer dyspepsia ". Laparotomy was performed for suspected perforation of the duodenal ulcer, but none was found. Three days after operation deep-vein thrombosis developed in the left leg.

In June, 1957, the patient again entered hospital having vomited " traces of blood ". The blood-pressure was 70/0 mm. Hg and, 2 pints of blood was transfused. The fæces, however, never showed more than a trace of occult blood; after transfusion the hæmoglobin level was 100%, and it seems very unlikely that there had been significant alimentary bleeding.

Throughout the period 1955–59 the patient had recurrent attacks of pain in the right hypochondrium, particularly at night, which radiated to the epigastrium and precordium and were usually associated with vomiting.

Events leading to Venous Ligation

In September, 1959, admission to hospital was necessitated by a further acute attack of pain succeeded by vomiting. The skin was pale and the pulse-rate rapid, but the outstanding physical finding was profound hypotension; blood-pressure 70/50 mm. Hg. Sweating was not conspicuous. Because of recent increase in swelling and tenseness in the left leg (the site of the previous deep-vein thrombosis) it was considered that the patient might have sustained a pulmonary embolus; this diagnosis was supported by the appearance in the recovery period of a loud systolic murmur in the pulmonary area which subsided gradually over the next two to three weeks (Hollister and Cull 1956).

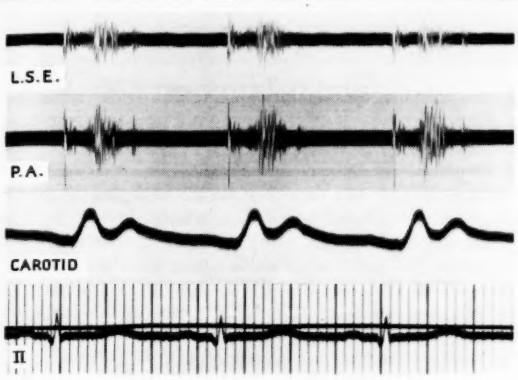
Despite long-term anticoagulant therapy the patient had an exactly similar illness in February, 1960, characterised by hypotension and the later appearance of a pulmonary systolic murmur. This time the patient had mild glycosuria on admission and was subsequently shown to have impaired glucose tolerance. After an oral dose of 50 g. glucose the blood-sugar values were as follows: Fasting 106 mg.; $^1/_2$ hr. 190 mg., 1 hr. 205 mg., $1^1/_2$ hr. 178 mg., 2 hr. 125 mg. per 100 ml. On this occasion pulmonary blood-flow and vascular pressures were measured while the heart murmur was still loud. Pulmonary arterial and wedge pressures were within normal limits, and the pulmonary blood-flow was 4·46 litres per minute. There was no evidence of any shunt, and the pulmonary-valve pressure gradient was normal. Pulmonary angiography was also normal.

Despite the negative findings it was believed that the patient had sustained another pulmonary embolus, and in view of the life-threatening nature of the two attacks that had been witnessed it was decided to undertake venous ligation. Accordingly, in April, 1960, the left external iliac vein was tied after intraosseous venous angiography had suggested the presence of narrowing in the distal part of this vein.

The Clinical Syndrome

The patient remained well for two months, but in June, 1960, she had another sudden attack closely resembling the first two. Other attacks followed, the pattern on each occasion being strikingly similar. They occurred in the evening, having been preceded by a feeling of apprehension lasting several hours. It was not possible to recognise any precipitating cause. The attack began with pain and vomiting. The pain was constant, mainly in the right hypochondrium radiating through to the back but also high in the epigastrium and in the precordial region. Vomiting and retching were intense, sometimes with slight blood-staining of the vomitus, and like the pain they persisted for some hours. It was usually two to three hours after the onset of the attack that the patient arrived in hospital.

She was always pale and had tachycardia, the pulse-rate being in the region of 100–120 per minute. The main physical finding was profound hypotension, blood-pressure readings of



Phonocardiographic findings.

L.S.E. = phonocardiogram left sternal edge. P.A. = phonocardiogram pulmonary area. Carotid = carotid pulse. II = electrocardiogram lead II.

70/50, 75/50, and 90/60 mm. Hg being typical. There was usually a considerable leucocytosis (e.g., 33,000 and 27,700 per c. mm.), the increase being mainly of neutrophil polymorphs. (A typical differential white count was as follows: neutrophils 86%, lymphocytes 12%, monocytes 2%.)

On the following morning the patient complained of pain and tenderness in the right hypochondrium which persisted for two to three days. Otherwise she seemed to have recovered; the pulse-rate, blood-pressure, and white-cell count had returned to normal values. On the third, fourth, or fifth day after the initial episode there developed a loud grade-v systolic murmur audible over the whole precordium but maximal in the pulmonary area, and sometimes accompanied by a thrill. It had the phonocardiographic characteristics of a pulmonary outflow murmur (see figure), and gradually subsided over the next two to three weeks.

Further Investigations

Various diagnoses were considered, including abdominal epilepsy, acute porphyria, or a secreting adenoma such as a carcinoid tumour or a phæochromocytoma. None seemed to explain the clinical picture; electroencephalography showed no abnormality, and urine analysis for 5-hydroxyindoleacetic acid, porphyrins, and catechol amines was normal. In a cholecystogram there appeared to be a soft-tissue mass above the right kidney. When pyelography, tomography, and aortography failed to confirm the presence of a tumour, the shadow was judged to be due to the quadrate lobe of the liver. The right kidney was low in position, but the significance of this finding was uncertain since a congenitally malformed duplex kidney was seen to be present on the left side.

In September, 1960, when laparotomy was being considered, the patient had an attack in hospital which was observed from the onset. The attack was a relatively minor one, but two new features were evident. At the outset the total white-cell count was 21,700 per c.mm., and on this occasion 69% of the cells were lymphocytes; the blood-pressure readings and pulse-rates were as follows: 7 P.M., B.P. 200/100 and pulse-rate 65; 7.20 P.M., B.P. 220/95 and pulse-rate 110; 7.45 P.M., B.P. 140/50 and pulse-rate 104; 8.10 P.M., B.P. 110/60; 8.40 P.M., B.P. 90/60 and pulse-rate 88; 9.30 P.M., B.P. 80/50, pulse-rate 70. Afterwards the patient recovered gradually, as in the previous episodes.

Urine collected after this attack contained an excess of catechol amines (approximately 250 μg. per 100 ml., expressed as noradrenaline base), when examined by the method of von Euler and Floding (1955). Although no further attack occurred, two out of three subsequent twenty-four-hour collections of urine contained greatly increased amounts of catechol amines (more than 100 μg. per 100 ml.). The third, which was assayed at the same time under identical conditions, contained less than 10 μg. per 100 ml. More detailed examination of one of these urine collections gave a value of 3500 μg. of adrenaline plus noradrenaline excreted in twenty-four hours (expressed as noradrenaline base); while paper-chromatography of the extract and comparison with known standards indicated that approximately 75% of the total was adrenaline, the remainder being noradrenaline. Only faint traces of other related compounds were seen on the chromatogram, and these could not be identified with certainty. In particular, hydroxytyramine was not detectable (McMillan 1957).

Laparotomy

Laparotomy was undertaken in October, 1960, by Prof. M. F. A. Woodruff. A transverse upper abdominal incision was made, and after difficulty occasioned by adhesions a tumour was exposed in the right suprarenal area. As soon as it was handled, the systolic blood-pressure rose to 220 mm. Hg, and an uncountable irregular tachycardia developed. During mobilisation and removal of the tumour, 65 mg. of phentolamine were required, by repeated intravenous injection, to keep the systolic blood-pressure below 150 mm. Hg. At this level there were no extrasystoles and the heart-rate was less than 100 per minute. There was no diastolic hypertension. After removal of the tumour the pressure abruptly fell to a systolic level of 80 mm. Hg; and a noradrenaline infusion was necessary, in reducing amounts, for five hours until the blood-pressure stabilised.

Postoperative recovery was uneventful, and the patient is now in excellent health (twelve months after operation). Urine examination since operation has shown normal excretion of catechol amines (approximately 10 μg. per 100 ml.).

The Tumour

The tumour was solid, measured $6{\cdot}5 \times 3{\cdot}5 \times 2{\cdot}5$ cm., and weighed 86 g. Its size and shape were very similar to the soft-tissue mass which appeared to lie above the right kidney on X-ray. It had the typical histological characteristics of a phæochromocytoma. Extraction of a portion of the tumour with 0·1 *N* sulphuric acid yielded 8 mg. of catechol amines, expressed as noradrenaline base, per g. of wet tissue. Paper-chromatography of the extract indicated that about two-thirds was adrenaline, the remainder being noradrenaline with a trace of hydroxytyramine.

Comment

Those phæochromocytomas which secrete noradrenaline and adrenaline in excessive amounts are usually found in direct connection with one of the adrenal glands (von Euler and Ström 1957, Goodall and Stone 1960), and of the suprarenal tumours two-thirds arise on the right side (Smithwick et al. 1950). In these respects the present case was not unusual. However, tumours in which the secretion of adrenaline greatly exceeds that of noradrenaline are rare (von Euler and Ström 1957, Goodall and Stone 1960). Cases in which hypotension has been encountered as part of the clinical picture are also excessively rare; Baird and Cohen (1954) and Gjøl et al. (1957) described cases in which hypotension alternated with wild excursions of pressure to hypertensive levels. Evans' (1937) patient died in shock. In none of these were the biochemical aspects well documented.

No previous case appears to have been described in which paroxysms of profound hypotension were the main finding, and the other clinical features of the present case also seem to be unique.

Most phæochromocytomas discharge noradrenaline or a mixture of noradrenaline and adrenaline in which the former predominates. The unusual clinical syndrome in the present case was associated with a tumour whose output and content of catechol amines consisted mainly of adrenaline. It is, therefore, of interest that most of the features which the patient presented have been produced

in animals and man by the experimental infusion of adrenaline:

1. The aura of *apprehension and fear* (Luft et al. 1950) is typical of hyperadrenalinæmia and is not found during the infusion of noradrenaline.

2. *Hypotension.*—Cannon and Lyman (1913) showed that small doses of adrenaline (0·1 ml. of 1/100,000 solution) produced hypotension in the cat, larger doses (0·2 ml.) a rise and then a fall in blood-pressure, and still larger doses (0.5 ml.) predominantly a rise. Recurrent injections of the smallest dose led to a progressive fall in the mean arterial pressure. Observations in man (Goldenberg et al. 1948) confirmed that infusions of adrenaline tend to cause a fall in peripheral resistance, in contrast to noradrenaline which produces a rise.

3. *Tachycardia.*—Noradrenaline administered by slow intravenous infusion causes bradycardia; adrenaline causes tachycardia (Goldenberg et al. 1948, Barcroft and Konzett 1949, De Largy et al. 1950).

4. *White-blood-cell changes.*—Infusions of noradrenaline do not significantly affect the total or differential white-cell count. Adrenaline causes leucocytosis mainly due to lymphocytosis initially (Luft et al. 1950); this is succeeded after two to three hours by a polymorph leucocytosis (French 1960).

5. *Impaired glucose tolerance.*—Many workers (see von Euler 1956) agree that adrenaline is much more active than noradrenaline in causing glycogenolysis and glycosuria.

6. *Pain and tenderness in right hypochondrium.*—Abdominal pain is occasionally reported in cases of phæochromocytoma (Smithwick et al. 1950) This pain has not been explained. In the present case, it seems unlikely that it was due to the tumour although this was located in the right upper abdomen. Adrenaline administered into the general circulation of intact animals or man usually increases the hepatic blood-flow greatly (Bearn et al. 1951, Bradley et al. 1952 Grayson and Johnson 1953) whereas noradrenaline has little effect. Possibly, therefore, in the present case, the pain and tenderness in the right hypochondrium were due to hepatic congestion.

7. *Heart murmur.*—Although both adrenaline (Witham and Fleming 1951) and noradrenaline (Goldenberg et al. 1948) are known to raise the mean pulmonary arterial pressure, this effect is unlikely to account for the auscultatory findings in the present case, in view both of the time relationship to the attacks and of the findings on cardiac catheterisation. The cause of the transient pulmonary murmur and thrill was not discovered.

Summary

A case is described in which paroxysmal hypotension was found to be due to a phæochromocytoma that was secreting mainly adrenaline. The other clinical features —namely, an aura of fear, tachycardia, white-blood-cell changes, impaired glucose tolerance, and pain and tenderness in the right hypochrondrium—are also compatible with the pharmacological action of adrenaline. A loud pulmonary systolic murmur which succeeded each attack has not been explained.

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REFERENCES

Baird, I. M., Cohen, H. (1954) *Lancet*, ii, 270.
Barcroft, H., Konzett, H. (1949) *ibid.* i, 147.
Bearn, A. G., Billing, B., Sherlock, S. (1951) *J. Physiol.* **115**, 430.
Bradley, S. E., Ingelfinger, F. J., Bradley, C. P. (1952) *in* Visceral Circulation (edited by A. A. G. Lewis and G. E. W. Wolstenholme); p. 129. London.
Cannon, W. H., Lyman, H. (1913) *Amer. J. Physiol.* **31**, 376.
De Largy, C., Greenfield, A. D. M., McCorry, R. L., Whelan, R. F. (1950) *Clin. Sci.* **9**, 71.
Evans, V. L. (1937) *J. Lab. clin. Med.* **22**, 1117.

References continued in next column

Preliminary Communications

IRRADIATION OF CEREBRAL ASTROCYTOMATA UNDER WHOLE-BODY HYPOTHERMIA

THE sensitivity of a variety of animal and plant tissues to X-rays is influenced to an important degree by the concentration of oxygen available to them at the time of irradiation.[1–5] This concentration is in turn influenced by reduction of temperature, which decreases consumption of oxygen but increases the amount dissolved in the tissues. Working with dogs, Bigelow et al.[6] noted a reduction of about 50% in oxygen consumption at 28°C, Drew et al.[7] a rise in venous oxygen saturation to 85% at 8°C, and Severinghaus [8] an increase in dissolved plasma oxygen of 50% at 20°C, and 20% at 30°C.

In 1959 one of us (L.W.) suggested that irradiation under hypothermia might be tried for patients with cerebral glioblastoma multiforme (astrocytoma grades III and IV [9]) in the hope of obtaining an increase in tumour radiosensitivity.

The prognosis for these patients is uniformly bad:

Earle et al.[10] report a six months' average postoperative survival for 167 patients with glioblastoma multiforme, and Craig et al.[11] a 6·6 months' average postoperative survival for 54 patients with grade-IV astrocytomata. Of 187 patients treated surgically, only 11 survived more than two years [12] and of 30 receiving radiotherapy [13] only 3 were alive after three years. Netski et al.[14] described 70 cases of glioblastoma multiforme of which 57 were treated surgically, and of these 35 received radiotherapy. They concluded that little benefit was derived from postoperative irradiation. Penman [15] finds that of 183 patients (grades III and IV astrocytomata) treated surgically but not irradiated approximately 61% had died within three months, 80% within six months, 90% within one year and 92% within eighteen months. Of 188 patients in whom similar surgical treatment was combined with postoperative radiotherapy, approximately 50% had died within three months, 62% within six months, 80% within one year, and 88% within eighteen months. Thus, at the end of eighteen months, the difference

1. Crabtree, H. G., Cramer, W. Eleventh Scientific Report of the Imperial Cancer Research Fund; p. 103. 1934.
2. Thoday, J. M., Read, J. *Nature, Lond.* 1947, **160**, 608.
3. Gray, L. H., Conger, A. D., Ebert, M., Hornsey, S., Scott, O. C. A. *Brit. J. Radiol.* 1953, **26**, 638.
4. Gray, L. H. *ibid.* 1957, **30**, 403.
5. Deschner, E. E., Gray, L. H. *Radiat. Res.* 1959, **11**, 115.
6. Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., Greenwood, W. F. *Amer. J. Physiol.* 1950, **160**, 125.
7. Drew, C. E., Keen, G., Benazon, D. B. *Lancet*, 1959, i, 745.
8. Severinghaus, J. W. *Ann. N.Y. Acad. Sci.* 1959, **80**, 384.
9. Kernohan, J. W., Mabon, R. F., Svien, H. J., Adson, A. W. *Proc. Mayo Clin.* 1949, **24**, 71.
10. Earle, K. M., Rentschler, E. H., Snodgrass, S. R. *J. Neuropath. exp. Neurol.* 1957, **16**, 321.
11. Craig, W. M., Dodge, H. W., Svien, J. H. *Minn. Med.* 1957, **40**, 471.
12. Davis, L., Martin, M., Goldstein, S. L., Ashkenazy, M. *J. Neurosurg.* 1949, **6**, 33.
13. Jones, A. *Ann. R. Coll. Surg.* 1960, **27**, 337.
14. Netsky, M. G., August, B., Fowler, W. *J. Neurosurg.* 1950, **7**, 261.
15. Penman, J. Unpublished results. 1961.

DR. RICHMOND AND OTHERS: REFERENCES—*continued*

French, E. B. (1960) Personal communication.
Gjøl, N., Dybkaer, R., Funder, J. (1957) *Brit. med. J.* ii, 673.
Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G., Roh, C. E (1948) *Amer. J. Med.* **5**, 792.
Goodall, McC., Stone, C. (1960) *Ann. Surg.* **151**, 391.
Grayson, J., Johnson, D. H. (1953) *J. Physiol.* **120**, 73.
Hollister, L. E., Cull, V. L. (1956) *Amer. J. Med.* **21**, 312.
Luft, R., Sjögren, B., Cassmer, O., Issen, E. (1950) *Acta Endocr., Copenhagen*, **4**, 153.
McMillan, M. (1957) *Lancet*, i, 715.
Smithwick, R. H., Greer, W. E. R., Robertson, G. V., Wilkins, R. W. (1950) *New Engl. J. Med.* **242**, 252.
von Euler, U. S. (1956) Noradrenaline; p. 214. Springfield, Ill.
— Floding, C. (1955) *Acta physiol. scand.* **33**, suppl. 118, p. 57.
— Ström, G. (1957) *Circulation*, **15**, 5.
Witham, A. C., Fleming, J. W. (1951) *J. clin. Invest.* **30**, 707.

in mortality following surgery alone and surgery combined with radiotherapy was less than 4%, the mortality in each case being around 90%.

Against this background of therapeutic failure we decided to make a clinical trial of the value of irradiation under hypothermia; and, because of the unexpected results and various dangers of this form of treatment, we are giving this preliminary report of our experiences with 14 patients. A preliminary trial with animals was considered; but any results from it would not necessarily apply to man, particularly in view of the conflicting reports concerning the influence of temperature on tissue radiosensitivity. Eighteen months ago, therefore, a small unit was established at the Royal Marsden Hospital to undertake a controlled trial of patients receiving radiotherapy (1) under conditions of mild hypothermia (30–33°C rectal temperature) and (2) at normal temperature.

In view of the very short expectancy of life for most of these patients, it was thought that significant differences in survival-times between these two groups soon would become apparent if the treatment were of any value.

SELECTION OF PATIENTS

For admission to the trial patients had to fulfil the following criteria:

1. They must have a histologically proven astrocytoma of malignancy grade III or IV (according to the separate and concurring opinions of three pathologists).
2. They must be in good general health without evidence of other disease and with only mild intellectual impairment or minimal limb weakness.
3. They must fall within the age-groups 30–39 or 40–49 years. Each of these age-groups was further divided by sex, producing four treatment groups.

All patients were treated surgically: as much as possible of the tumour was removed and a good decompression achieved, thus giving the patient a reasonable chance of surviving the period over which irradiation would be given. Within each subgroup alternate patients were treated at normal temperature and under hypothermia. In view of the small number of patients, the results were to be assessed by sequential analysis.

The next-of-kin of each patient was interviewed, the prognosis for the patient was discussed, and the possible dangers of long-continued hypothermia were clearly presented before permission to treat the patient was accepted.

METHOD

Radiotherapy

Owing to difficulties in transporting patients under hypothermia to the 2MeV Van de Graaff generator it was decided to use the more readily accessible deep X-ray units (factors: 250 kV; 15 mA; half-value layer 3·4 mm. copper; dose-rate 32 r per min.). Previous experience in the treatment of cerebral astrocytomata of grades III and IV had shown that small-field or medium-field techniques did not cover the whole of such lesions.[16] Whole-brain irradiation was used both to ensure that all the tumour was included in the volume irradiated and to simplify the treatment technique for patients under hypothermia. Two parallel opposing lateral fields, 20 × 15 cm., were employed, and an incident dose of 150r was given to both fields daily on six days a week, the aim being to achieve a total mid-line dose of approximately 4000r in five weeks, provided it was found to be safe to maintain the cooled patients under continuous hypothermia for so long.

Hypothermia

Simple whole-body cooling with icebags was used, and the rectal temperature maintained at 31–32°C with the aid of pethidine, promezathine, and chlorpromazine. Though rectal and brain temperatures differ, the rectal recording was regarded as a satisfactory guide to temperature control, since long-continued hypothermia would give enough time for equilibrium in temperature gradients to be established. Certainly the rectal, oral, and axillary temperatures change in close parallel over these long periods. The corresponding brain temperature remains to be determined.

Except in the first few cases, hypothermia was induced under general anæsthesia, and the patient was usually permitted to regain consciousness at the reduced temperature before the first irradiation treatment was given.

RESULTS

Cooled patients clearly showed an increased response to irradiation, some of them within a few hours of receiving the first 150r to each hemisphere, and in most of the patients to whom a total dose of 300–450r was given over a period of two to three days. Two patients were treated with lower doses, one receiving 50r daily and the other beginning with 50r and increasing this daily by 25r, but they showed the same increased response after receiving total incident doses of 200r and 225r, respectively, to both sides of the head.

In these circumstances we could no longer conduct a controlled clinical trial, since the irradiation dosage would have to be different in the two groups of patients. We decided, therefore, to pursue the clinical problem of irradiation under hypothermia, and, with the complications of long-continued hypothermia more clearly appreciated, to include patients of all ages, provided their general health was good.

Patients irradiated under conditions of mild hypothermia developed signs of an acute cerebral reaction, varying from slight drowsiness and confusion or mild hemiparesis to deep coma with fixed dilated pupils and flaccid tetraplegia, the onset varying from a few hours to two to three days after the first irradiation. After such deterioration the patients were treated with urea solution (50 g. in 180 ml. of water through a Ryle's tube) and improved, usually within an hour. The improvement, however, was not always maintained unless further urea was given:

One patient became very drowsy some ten hours after her first treatment (150r incident to each hemisphere); but, having recovered spontaneously from this, she was given a further treatment on the following day. After five hours she became acutely restless, and after a further hour she was in deep coma. She was given urea and after three-quarters of an hour was responding to painful stimuli. An hour and a half after that she was alert and cooperative, and after another three hours she was smoking a cigarette. Radiotherapy was discontinued, but on the following afternoon she again became drowsy and passed into coma. This was relieved by urea, but there was a further episode of coma on each of the next two days before control was eventually established.

The clinical picture may be further and disturbingly complicated by gastric dilatation and ileus (with attendant problems of fluid and electrolyte balance) and by respiratory depression, of central origin, resulting in slow jerky respirations and poor respiratory excursion—an ideal background for infection. These complications—particularly those relating to the alimentary tract—may precede drowsiness and coma, so that by the time the latter occurs the patient may have become very ill indeed. Unlike the cerebral reactions, skin changes were never severe.

At first, we found it hard to believe that these doses of irradiation were large enough to produce the grave deterioration observed in our patients, in all of whom large decompressions had been made and most of whom were

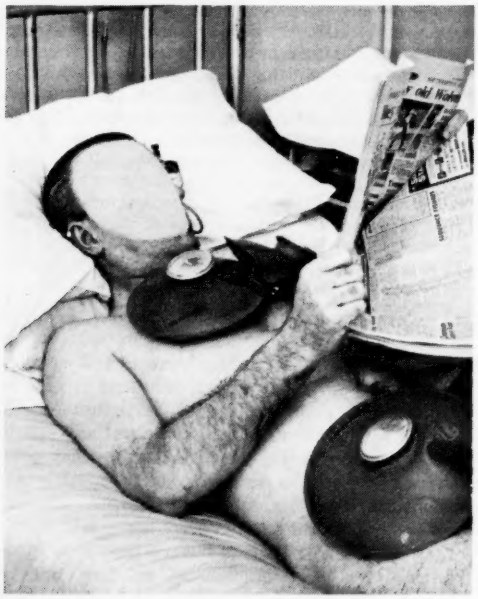
16. Concannon, J. P., Kramer, S., Berry, R. *Amer. J. Roentgenol.* 1960, **84**, 99.

alert before irradiation. The clinical response, however, has been consistent, even though the interval between the induction of hypothermia and the onset of irradiation was varied from a few hours to as long as seven days. Deterioration has always followed irradiation under hypothermia, but it has not followed hypothermia alone.

At normal temperatures severe clinical deterioration has not been seen after use of the fractionated doses of irradiation employed here—except occasionally in the presence of raised intracranial pressure. In our experience it is usual for patients, after decompression, to tolerate whole-brain irradiation at normal temperature without serious sequelæ, a mid-line dose of 4000r being given in five weeks, using a daily incident dose of 150–200r to both sides of the head.

In the absence of irradiation, patients under continuous mild hypothermia (30–33°C) remain alert and rational (see figure) except for inattention, unawareness of the passage of time, impairment of memory, and (later) complete inability to recollect the episode of hypothermia. One factor limiting the duration of mild hypothermia is a progressive fall in blood-platelets. For most patients, two weeks' mild hypothermis is safe, but a slight fall in platelets may continue for the first few days after rewarming. Platelet-counts of less than 100,000 per c. mm. have been seen in 4 patients after seven to ten days' hypothermia. However, owing to the very severe effects of two to three days' irradiation under hypothermia we were not faced with the problem of prolonging hypothermia for more than a few days.

Because serious sequelæ had resulted from only 150–300r, incident to each hemisphere, we decided to limit the total dose to 300r to each hemisphere, lest a higher dose might cause fatal complications. This perhaps explains why in 2 patients no clinical response was observed. Recently, with more experience of hypothermia, both with and without irradiation, we have given a further dose of 150r to all patients not showing a response after 300r; and so far this has not failed to produce some degree of cerebral reaction.



Man aged 42. 4th day hypothermia (without irradiation). Rectal temperature 29·8° C.

When slow deterioration is superimposed on initial dysphasia and dyspraxia, interpretation of the clinical picture may be difficult. In these circumstances irradiation has sometimes been continued though retrospective examination of the clinical notes shows that deterioration had already begun. One patient who received an extra 150r suffered no serious harm; but another, in whom it was difficult to be convinced that non-cooperation resulted from slow deterioration and mild paresis rather than from the initial dysphasia and dyspraxia, received a further three treatments resulting in marked deterioration from which he made only a very slow recovery.

Other results indicating an increased response to irradiation under hypothermia have been obtained by Bloom and Dawson [17] working with whole-body irradiation in mice at temperatures (29–37°C) which have included the same range as that used for this clinical trial (30–33°C) (see table). Judging by their experience, the increased effect of irradiation under hypothermia may occur only within a limited temperature range, since, in mice exposed to whole-body irradiation, the lethal effect increased from 37°C down to 31°C but at 29°C there were no deaths within the period of observation.

EFFECT ON MOUSE SURVIVAL OF COMBINED HYPOTHERMIA AND 550r TOTAL BODY X-IRRADIATION (BLOOM AND DAWSON [17])

Temperature	Number of mice	Survivals	% died
29°	19	19	0
31°	19	7	63
33°	18	11	39
35°	18	13	28
37°	21	18	14

Our experience is contrary to that of many workers who report (in rats and mice) a radioprotective effect of hypothermia [18–20]; but their reports refer to lower temperatures (14–15°C, 20–23°C and 1°C) than we have employed. Crabtree and Cramer [1] demonstrated an increased radiosensitivity of mouse carcinoma tissue at 0°C and noted that this could be eliminated if the tissue was irradiated under anaerobic conditions. Similarly, tissues irradiated at 37·5°C were less sensitive under anaerobic than aerobic conditions. These workers concluded that the differences in radiosensitivity were related to respiratory changes—due in the one case to reduction in temperature and in the other to the anaerobic environment.

Interpretation of our results is obviously difficult, but the facts are these:

1. In patients suffering from cerebral gliomata irradiation of the brain under mild hypothermia has produced a clinical effect not observed at normal temperatures with a comparable dose. This effect, whatever its mechanism, results in signs of an acute cerebral reaction (dilated pupils, paresis, &c.) which in the first instance are referable to the side of the brain in which the tumour is situated.

2. These signs may be reversed by the administration of urea solution, suggesting that the immediate effect of irradiation under hypothermia, in these patients, is cerebral œdema.

3. Although the localisation of signs at the onset of deterioration suggests that this effect may act primarily on the residual tumour, it is clear, both from the animal experiments referred to and from the results of higher dosage noted in some patients, that the normal brain tissue also may shew increased radiosensitivity under hypothermia.

17. Bloom, H. J. G., Dawson, K. B. *Nature, Lond.* 1961, **192**, 232.
18. Hajdukovic, S., Herve, A., Vidovic, V. *Experimentia*, 1954, **10**, 343.
19. Kuskin, S. M., Wang, S. C., Rugh, R. *Amer. J. Physiol.* 1959, **196**, 1211.
20. Weiss, L. *Int. J. Rad. Biol.* 1960, **2**, 409.

In two patients who died shortly after treatment there were acute degenerative changes in the tumour tissue but no obvious changes in the normal brain tissue apart from the œdema often seen round malignant gliomata. Although similar changes occur spontaneously in these tumours the important fact is that in spite of severe clinical deterioration, any gross changes (macroscopic and microscopic) were confined to the tumour.

4. There is no evidence that life has been prolonged by the treatment in its present form.

SUMMARY AND CONCLUSIONS

1. 14 cases of cerebral glioblastoma multiforme (astrocytoma grades III and IV) have been treated by irradiation under mild hypothermia (30–33°C).

2. Evidence is presented which suggests that under hypothermia cerebral tissues become more sensitive to X-rays. A differential sensitivity, favourable to treatment, may exist between tumour and normal tissue cells.

3. Because irradiation under hypothermia is followed by signs of acute cerebral œdema, the total incident dose to each hemisphere, in any single course of treatment, has had to be limited to 300–450r (given as 150r daily). With this dose it has not been possible to prolong life beyond what would be expected from surgery alone. An attempt is being made to increase the total dose of irradiation—either by giving several courses of treatment or by diminishing the size of the fields.

4. Experiments on mice support the view that mild hypothermia increases tissue radiosensitivity.

5. Well-oxygenated tissues are considered to be practically at their maximum sensitivity and no appreciable increase in response to irradiation is expected to follow a further rise in oxygen tension.[21] Because of the more generalised cerebral reactions in some of our cases, and the rise in mortality in mice after total body irradiation under hypothermia, it appears likely that the increased response to irradiation during mild hypothermia is not entirely due to an increase in oxygenation of the tissues.[16]

6. Although cerebral œdema is poorly tolerated owing to the harmful effects of raised intracranial pressure and the total dose of cerebral irradiation under hypothermia thereby severely restricted, this limitation may not apply to the treatment of tumours at other sites in the body where a higher dose may be achieved and better results obtained. However, in view of the unexpectedly severe reactions reported here it would be advisable to use low dosages in commencing any course of treatment involving irradiation under hypothermia.

We should like to thank Mr. Wylie McKissock for his advice and encouragement in carrying out this work, Mr. Alan Hunt for his support, and the Matron and the nursing staff at the Royal Marsden Hospital for their considerable cooperation, and the Dept. of Medical Photography, Royal Marsden Hospital, for the photographs.

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21. Gray, L. H. Lectures on the Scientific Basis of Medicine; p. 314, London, 1957.

USE OF DIMERCAPROL OR PENICILLAMINE IN THE TREATMENT OF CYSTINOSIS

MANY enzyme systems depend on the presence of free thiol groups. Where disulphide is present in gross excess, it may enter into generalised exchange reactions with thiols, and so cause loss of enzyme and other functions. That this may happen in cystinosis is supported by the observations recorded here.

The discovery that thiol groups are essential factors in dehydrogenase systems suggested that oxidative processes —especially perhaps those of the citric-acid cycle— would be inhibited by excess of intracellular cystine. This has been substantiated (1) by the demonstration of almost total lack of succinic dehydrogenase activity in fresh necropsy samples of cystinotic liver, and its reactivation by pre-incubation with cysteine, and (2) by the finding that in cystinosis blood-levels of pyruvate are abnormally high, both in the fasting state and after a dose of glucose (Payne-Poulton scale).

Routinely, fingerprick samples of blood were taken 60 minutes after the glucose drink, and pyruvate was estimated by the Friedemann and Haugen method.[1] In four patients with cystinosis the range was 1·46–2·24 mg. per 100 ml. whole blood (mean 1·95 mg. per 100 ml., 14 estimations) compared with 0·82–1·40 mg. (mean 1·00 mg., 11 estimations) in normal children and adults. Keto-acid chromatography in one patient showed a rise also in the blood and urine levels of α-oxoglutarate (a further substance requiring a thiol-dependent oxidation).

In view of the presumed causative effect of cystine in these metabolic anomalies, we have given thiol compounds in cases of cystinosis in the hope of reactivating or maintaining thiol-dependent systems. The compounds used were dimercaprol (BAL), given by intramuscular injection in doses of 3·0 mg. per kg. body-weight, and penicillamine by mouth, 100 mg. t.d.s. Initial doses were given on each of 3 consecutive days, and thereafter maintenance dosage every 10th day with dimercaprol, or every 17th day (lately increased to every 6th day) with penicillamine. This was the basic treatment. With further experience the regime will doubtless be modified to suit individual needs.

CLINICAL OBSERVATIONS

Three patients have been studied. Patients 1 and 2 are sisters, aged 2 years 4 months and 3 years 9 months respec-

1. Friedemann, T. E., Haugen, G. E. *J. biol. Chem.* 1943, **147**, 415.

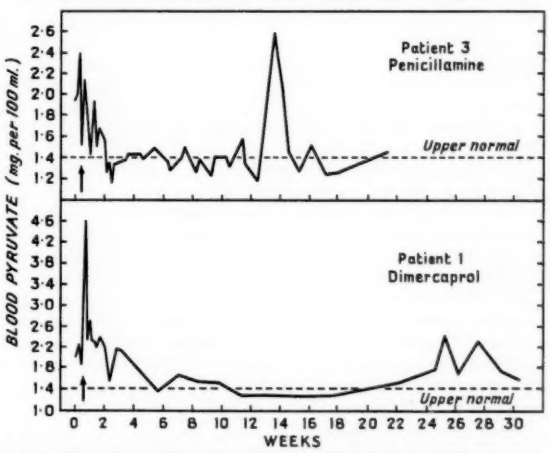

Fig. 1—The effect of dimercaprol or penicillamine on blood-pyruvate level. Treatment begun (↑).

tively, and patient 3 is a girl aged 3 years and 2 months. All were severely affected, and were being managed with alkali therapy; patients 1 and 2 also received vitamin-D supplements.

Fig. 1 shows the effect of treatment on blood-pyruvate levels in patients 1 and 3. After an immediate sharp increase following the initial doses, the levels fell to upper-normal values, or nearly so. The sharp peak observed with patient 3 after 13 weeks coincided both with an attempt to reduce the management dose of Albright's mixture, and with a respiratory infection and abdominal pain. This rise seems to be attributable mainly to the infection, since it disappeared with the disappearance of symptoms, even though the citrate mixture was maintained at only half of the original dose.

The rise seen in patient 1 after 26 weeks' treatment is unexplained, but may have been due to the dose of dimercaprol becoming inadequate in a child who was gaining weight. The dose was increased in accordance with this rise in weight, and pyruvate levels show some signs of returning to normal. On the other hand, the increase observed might be due to drug tolerance.

Patient 2, treated with dimercaprol for 17 weeks, has so far shown no regular response in blood-pyruvate level, normal

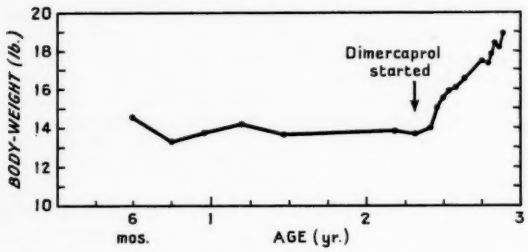

Fig. 2—Growth response of patient 1 to dimercaprol treatment.

levels for several weeks being followed by sudden increases. This child was the oldest to be treated; so this failure to maintain the response may represent a stage of progressive impairment of enzyme systems at which correction of thiol-disulphide imbalance is no longer possible.

It has been mentioned that high levels of α-oxoglutarate were found in one case (patient 1). With dimercaprol treatment an initial increase was observed (as found for pyruvate), followed by a decrease to normal values.

Renal Effects

Evidence of an improvement of renal function with respect to the aminoaciduria was seen in patients 2 and 3 (abnormal aminoaciduria was absent in patient 1). After the initial treatments a diminution of the gross generalised aminoaciduria was observed, the pattern being almost normal in patient 3 after 2 weeks. Alanine and glutamate were the first to respond to treatment and the first to reappear in abnormal amounts as the effect of treatment was lost. This could be explained by the role of these aminoacids as immediate precursors of pyruvate and α-oxoglutarate, respectively, the further metabolism of which is blocked.

Other renal effects cannot yet be assessed accurately. Glycosuria was not pronounced in any of the cases, and urinary phosphate excretion was abnormally low in the presence of hypophosphatæmia in patients 1 and 3. Blood-urea was not raised before treatment in patient 1 and has remained unchanged, but the high blood-ureas seen in patients 2 and 3 before treatment have shown a steady fall. A puzzling feature, seen in all cases, was an immediately increased polyuria, which has continued throughout treatment, though the urgency of the patients' demands for drinks has been much reduced.

Acidosis

A further metabolic response was reduction of acidosis in patients 1 and 3, though not in 2; acidosis had been a recurring feature in spite of management with alkalis. The total-CO_2 value in patient 1 increased from 15 to 19 mEq. per litre (normal value for fingerprick blood = 20–25 mEq.) to 26, 27, and 24 mEq. for the 3 consecutive days of initial dimercaprol treatment. The total-CO_2 value in patient 3, which just before treatment was 18, 16, 16, and 15 mEq. per litre, immediately improved to 22, 24, 20, 21, 21, and 22 mEq. after penicillamine, and it has since been fairly well controlled, except during two infections, while being managed on half the previous alkali requirement.

In general wellbeing there has been considerable improvement in all the children, particularly in patients 1 and 3. They have been much more cheerful and active, and appetites have improved. The pronounced weight-gain of patient 1 is shown in fig. 2. Weight gain in the other children has been very slow, but it may be becoming more rapid. The total lengths of treatment for patients 1, 2, and 3 have been 7, 4, and 6 months, respectively, so far.

CONCLUSION

In certain cases of cystinosis treatment with dimercaprol or penicillin is followed by some improvement of metabolic function and clinical status. The corrective influence of these compounds is related to their capacity for reactivating impaired thiol systems.

In the three cases reported here the effect was encouraging, considering the ages of the children, and it would be of interest to test these drugs in early cases. The renal anomalies of the Fanconi syndrome might then be studied in relation to the generalised metabolic failure (particularly with regard to utilisation of pyruvate for energy) resulting from inhibition of thiol systems by cystine.

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Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION AND ITALIAN SOCIETY OF ORTHOPÆDIC SURGERY AND TRAUMATOLOGY

THE annual meeting of the British Orthopædic Association was held jointly with the Italian Society of Orthopædic Surgery and Traumatology in London on Sept. 28–30. Mr. H. J. SEDDON, president of the Association, was in the chair.

Tibia Vara

Mr. J. S. R. GOLDING (Jamaica) reported his findings in a series of 31 cases of tibia vara. He divided these into infantile and adolescent types. The former was first seen in tiny infants, and the latter between the ages of 6 and 13 years. Of his series 28 had been in the infantile group and 3 in the adolescent. There was no evidence of rickets or syphilis, but the patients were usually over-weight. The proximal epiphysis was affected in its posteromedial part, where growth was interfered with. This produced varus, internal torsion, and flexion. X-ray examination showed early changes in the medial part of the epiphysis line. Because of the depressed growth of the medial part of the epiphysis the joint appeared to be widened on this side. The medial tibial cortex became thickened. Fusion of the epiphyseal line medially occurred at puberty, but the lateral side continued to grow and the ultimate deformity was often gross. Treatment was by osteotomy as early as

possible. If full correction was obtained there was no recurrence. The adolescent type was much less severe, and osteotomy could be delayed until growth ceased.

Dr. W. BLOUNT (Milwaukee) said that corrective osteotomy was often made difficult by the ligamentous laxity on the medial side. Osteotomy was better than the unilateral use of staples. Early correction gave good results.

Dr. LEO MAYER (New York) said that the adolescent type was more common in his experience. When doing an osteotomy, growth of the upper fibular epiphysis should be stopped.

Lumbosacral Fusion

Mr. D. FREEBODY (London) presented a film describing his operation of anterior spinal fusion, which since 1955 he had performed 47 times for spondylolisthesis and 3 times for disc degeneration. The transperitoneal approach gave the best access to the lumbosacral joint. The great vessels could easily be retracted so that the danger of hæmorrhage was not great, and this was further reduced by improved anæsthetic techniques inducing hypotension. A massive graft was cut from the iliac crest and was keyed into a special slot cut in the 5th lumbar and 1st sacral vertebral bodies where it locked, after the disc had been excised, and it was packed round with bone chips. The patient was immobilised on a plaster bed for a month, and was subsequently in a plastic jacket for three months. Complications were a very few deep-vein thromboses, paralytic ileus, and stiffness of the back which was treated safely by manipulation at a later date. All the results were satisfactory.

Osteoarthritis of Hip

Mr. D. M. RIDDELL (London) and Mr. J. R. PEARSON (Manchester) had reviewed 400 patients with "primary" osteoarthritis of the hip who had not been subjected to operation. Two types could be defined—the adduction laterally rotated types, and the non-adduction type. In the two types the initial findings were similar, with loss of medial rotation and extension leading to contractures. In the adduction lateral-rotation type, which comprised 311 of the series, adduction, flexion, and lateral contractures developed, and subluxation might occur. The radiological changes were narrowing of the upper part of the joint followed by sclerosis and cyst formation. In the non-adduction type, abduction was lost and the hip finally assumed a flexed, laterally rotated position. Central subluxation might develop. The femoral neck was usually varus. With the former type the inferior capsule became thickened, and with the latter the posterior superior capsule was affected.

Mr. A. G. O'MALLEY (Liverpool) said that his investigations had led him to believe that in so-called primary osteoarthritis of the hip the soft-tissue contractures were primary and not secondary as was generally supposed. This shortening caused crushing of the articular cartilage. The iliopsoas muscle was the main cause of the contracture. He had divided this muscle 131 times in 119 patients since June, 1959; in 88% there had been relief of pain and, in some, improvement in movement and even in the radiological appearance. The operation should be done early to avoid gross changes. An advantage of the operation was the short period of convalescence—two days in bed and fourteen days in hospital. In patients with a gross adduction deformity an adductor tenotomy was necessary. He believed that congenital dislocation of the hip was also caused by a contracture of the psoas muscle, and in difficult cases this should be divided.

Congenital Coxa Vara

Prof. O. SCAGLIETTI (Florence) said that there were two types of congenital coxa vara—one in which the epiphyseal line was oblique, and the other in which it was vertical. The normal neck-shaft angle was 130°. 110° represented mild, and 85° severe, coxa vara. The neck-shaft angle should be restored to normal by means of an osteotomy which would restore leg length. Through a lateral incision the femur was divided between pins in the intertrochanteric region. The fragments were then angulated until the cut end of the distal fragment was opposed to the cortex below the greater trochanter. A plaster spica was applied with the pins incorporated and was retained for six months. If the neck-shaft angle was less than 85°, the greater trochanter was detached and reattached lower down.

Relapsed Club-foot

Mr. F. C. DWYER (Liverpool) said that the persistence of a small inverted heel in a club-foot was a primary factor in provoking relapse. The tendoachillis pulled on the inner side aggravating the deformity, and the weight in walking was taken on the outer side, so that the plantar fascia was never properly stretched. This deformity was corrected by an operation in which the os calcis was osteotomised on the medial side and a graft taken from the upper end of the tibia was inserted. The tendoachillis was lengthened by a Z-plasty. Skin closure presented a problem, but close tight suturing was preferable to any plastic procedure even if healing was delayed. Plaster was retained for ten weeks.

Sacro-iliac Tuberculosis

Mr. F. G. ST. CLAIR STRANGE (Canterbury) described the prognosis in sacro-iliac tuberculosis based on a study of 329 patients treated between 1920 and 1960. Follow-up of a significant number over five to thirty-eight years largely confirmed the conclusion reached in a ten-year survey of 176 cases in 1940. He emphasised the importance of this condition being considered when investigating low back pain and sciatica, particularly in young adults. Dividing the cases into four groups, he gave the following results, which showed the influence of antibiotics:

Group	*Mortality-rate (%)*	
	Overall	*After 1940*
Closed isolated lesions	5·4	5
Sinuses in isolated lesions	27·1	0
Closed multiple lesions	36·4	5
Sinuses in multiple lesions	58·6	8

Healing was usually sound and allowed normal work and play in most instances, though one-third of sinuses persisted or recurred. Late backache and relapse had been remarkably uncommon, and he could find little to commend arthrodesis because the result in 73% of cases was a sound spontaneous bony ankylosis. In 54 pregnancies in 24 women there had been no reactivation, and he dismissed termination of pregnancy and sterilisation in the handling of those with healed lesions.

Acute Osteomyelitis

Mr. N. H. HARRIS (London) said that in recent years the treatment of acute osteomyelitis had been yielding less and less satisfactory results. This deterioration was largely due to operative interference being delayed. With an increase in the incidence of organisms insensitive to penicillin, early operation was necessary to obtain the infecting organism so that an effective antibiotic might be given. It was quite wrong to delay surgery for long in order to observe the effect of the antibiotic. If the patient was admitted more than forty-eight hours after the onset, operation should be undertaken without delay. Incision of the subperiosteal abscess or aspiration of the bone was inadequate. The bone must be drilled to beyond the infected area. Patients treated within three days of onset should make an uneventful recovery. Osteomyelitis of the spine behaved quite differently. It could always be treated conservatively, even if the onset of the treatment was greatly delayed. Mr. SEDDON said that he agreed with everything that had been said. Since the early days of treatment with penicillin and drainage described by Trueta, resistant organisms, which made early operation even more urgent, had appeared, and we had forgotten what had happened in the past. Prof. J. TRUETA (Oxford) said that it was very gratifying to find fresh experience verifying his earlier findings. The Association should take a hand in making the urgency of treatment known to all.

Congenital Dislocation of Hip

Mr. G. P. MITCHELL (Edinburgh) said that it was necessary to know the degree and type of displacement of the congenitally dislocated hip, to determine the treatment and assess the results. This was possible only by means of an arthrogram, which was done routinely in all cases. Whenever interposition of soft tissue was seen an arthrotomy was performed. In all cases an inverted limbus was found, and occasionally a synovial fold as well. The type of displacement could be divided into primary instability with minimal displacement, partial displacement, and complete displacement, which could be either tight or loose. When complete displacement was present the limbus was always inverted, and in the loose type this was overlaid by a synovial fold which was often replaced when the hip was reduced on the frame. In these cases arthrotomy was always necessary; but in partial displacement, while the limbus was pressed upwards, there was no obstruction and it would respond to conservative reduction.

Genetic Factor in Dupuytren's Disease

Mr. R. S. M. LING (Edinburgh) said that in order to obtain accurate information about the familial distribution of Dupuytren's disease he had investigated the families of 50 affected patients. He had examined in all 837 relatives. There was definite evidence of the disease in 34 families, and no evidence in only 2. This 68%, and probably more, of the cases were familial. Dupuytren's disease was a disorder of the elderly. In all, 150 cases (16·9%) were found. 23% were over the age of 15, and 52% were over the age of 60. A strong genetic influence was found, which seemed to indicate a single gene as a mendelian dominant; this was of fundamental importance in the development of the disease.

HEBERDEN SOCIETY

THE Heberden Society met in London on Oct. 6.

Tyrosine Metabolism in Rheumatoid Arthritis

Dr. J. N. MCCORMICK, Dr. R. ROBINSON, Dr. P. SMITH, and Dr. J. DAY (Stoke Mandeville), using paper partition chromatography to investigate the urinary excretion of phenolic acid, had detected two abnormal substances in some patients with rheumatoid arthritis. One was still unidentified, while the other was the abnormal tyrosine metabolite *p*-hydroxyphenyllactic acid. In 29 (40·3%) of 72 cases of rheumatoid arthritis *p*-hydroxyphenyllactic acid was found, while it was present in only 2 (9·1%) of 22 cases of other rheumatic disorders, 4 (6·8%) of 59 hospital controls, and 1 (1·8%) of 55 healthy people.

Chronic Rheumatic Fever

Dr. M. R. MODY, Dr. B. M. ANSELL, Prof. E. G. L. BYWATERS, and Dr. G. T. G. THOMAS (Taplow) had applied the term "chronic" to cases of rheumatic fever where there was evidence of rheumatic activity for more than six months. This was found in 106 (11%) of the 902 cases admitted between 1947 and 1954. Of these, 58 were seen among the 646 first attacks, and 48 in the 256 patients who had had at least one previous attack of rheumatic fever or chorea. A comparison group, matched only for first and second attacks, was drawn from patients admitted over the same period. On initial examination the prevalence of carditis was greater in those in whom the disease subsequently remained active for a long time, and the carditis was also more severe. This state persisted up to the time of discharge and at the five-year follow-up. The only other distinguishing clinical feature was a higher incidence of nodule formation in those in whom disease become chronic (58% compared with 22%). The mortality in hospital was 7·5% in those with long-continued activity and 1·9% in the comparison group, and this difference was even greater at the five-year follow up.

Steroid Therapy

Dr. N. BENNETT JONES (Liverpool) suggested that in the management of steroid-treated patients requiring surgery, until a reliable and easily applied test of adrenal responsiveness to stress was evolved, it would be wise to prescribe prophylactic steroids for patients who had previously been treated with corticosteroids, to increase the dose for those already on these drugs, and to be prepared to treat energetically adrenocortical failure should it develop.

Long-term Corticosteroid Therapy

The Heberden Round was given by Dr. OSWALD SAVAGE, who remarked on the differences on side-effects between oral corticosteroids, with their high incidence of dyspepsia and bruising, and corticotrophin, with which hypertension, acne, and resistance were the commonest problems. It seemed possible that corticotrophin might be withdrawn more easily.

Reviews of Books

The Vesico-Vaginal Fistula

J. CHASSAR MOIR, M.D., LL.D., F.R.C.S.E., F.R.C.O.G., Nuffield professor of obstetrics and gynæcology, University of Oxford. London: Baillière, Tindall, & Cox. 1961. Pp. 168. 40*s*.

OVER the past thirty years Professor Chassar Moir has had a particular interest in urinary fistulæ, and difficult, complicated, and supposedly intractable cases have been sent to him by colleagues from many parts. Many British gynæcologists and their patients have reason to thank him for his patience, persistence, and technical skill.

This important monograph, which is certain to rank among the classical contributions to gynæcological literature, is based on his experience of 230 cases of urinary fistulæ, in many of which there had previously been an unsuccessful attempt at repair. The introductory chapter contains an interesting account of the work of J. Marion Sims, the great American surgeon. There follows a description of the types of fistulæ seen in the Oxford clinic; three-quarters of the lesions followed some gynæcological procedure and the remainder were obstetric. Mostly they were traumatic bladder fistulæ, but there were 40 instances of complete urethral destruction or of radium necrosis. Later chapters deal with the principles of treatment, the choice of instruments, the various techniques used by the author, and the care of the patient before and after operation. Simple procedures are most often satisfactory, but modifications or alternatives may occasionally be required and these are described. Throughout the book vaginal methods of repair are emphasised, but one chapter is devoted to transabdominal and transvesical operations. Professor Chassar Moir is adamant that the suprapubic approach has a very limited place in fistula work. The results of treatment are analysed, and he shows that in the absence of active malignant growth there is every chance that a vesicovaginal fistula can be satisfactorily and permanently cured by surgery.

Cerebral Palsy in Childhood and Adolescence

J. L. HENDERSON, M.D., F.R.C.P.E., professor of child health, University of St. Andrews; consultant pædiatrician, Eastern Regional Hospital Board, Scotland. Edinburgh: E. & S. Livingstone. 1961. Pp. 403. 35*s*.

ALL who are interested in cerebral palsy know well that the Scottish Council for the Care of Spastics has, since its foundation in 1946, persistently hunted for the truth about this not so rare disability. This book gives in detail many of the findings in this field survey of the condition as it exists in the Eastern hospital region of Scotland, which is half urban and half rural, and therefore representative of Scotland as a whole. It does not pretend to be a textbook on cerebral palsy, and it is interested only in facts which have been proven. In it there are no muddled thinking and no false hopes, but it exposes many loose ends which must be looked for and tied before the best treatment of a patient with this type of brain damage can be established. Particularly useful are the chapters on ophthalmic and dental complications, for they offer a new approach in

dealing with the patient as a whole individual. The doctor has known for the past century that the orthopædic surgeon may help his patient, but today even parents recognise the need for hearing assessment as well as special educational and social care. This book impresses by its message that only teamwork will do—and teamwork for the duration of the patient's life.

The facts and figures may well act as a stimulant to all those who are dealing with a number of the 2 per 1000 children who suffer from cerebral palsy. The publishers are to be congratulated on the clear presentation of the many tables which have been needed to set out the findings of the survey.

Preventive Medicine in World War II

Vol. 5. *Communicable Diseases Transmitted through Contact or by Unknown Means.* Editor in Chief: Colonel JOHN BOYD COATES, Jr., M.C. Washington: Office of the Surgeon General. 1960. Pp. 530. $5·75.

WE found much to praise[1] in the previous volume of this great undertaking, and this is equally interesting. It consists of a series of essays each dealing with a disease or group of diseases. The military history of each disease, the incidence in the American Armed Forces during the war, the relevant experimental work, the progress in methods of control which developed during the war, and an assessment of the disease as a military hazard: these are the framework of each essay, and the general standard is what can be expected from a group of authors which includes J. R. Paul, Albert Sabin, and Joseph E. Smadel. The longest section is on the venereal diseases, and the general conclusion is that knowing all we do of the general and specific causes of these infections and having adequate methods of treatment we are still unable to devise a tolerable method of prevention—and the accent is on "tolerable". Wherever the American soldier went the problem had to be considered afresh. Control was difficult in North Africa, harder in Sicily, and almost impossible in Naples. When coloured troops were stationed in West Africa their infection-rate soon rose to more than 100% per annum. In every theatre V.E. and V.J. days were followed by a sharp increase in infections. Contrary to the current forecasts, the closing of brothels was almost always followed by a lowering of the infection-rate. Much thought and money were put into propaganda but the benefits were not obvious.

Schistosomiasis due to *Schistosoma japonicum* became a problem during the campaign in the Philippines: the interest of this story lies largely in the attempts (which were not very successful) at teaching the soldiers that immersion in natural waters was dangerous. Epidemic keratoconjunctivitis was recognised at a time when most of us had other things to think about, and since prevention is not difficult, it is now almost forgotten. Its importance as a military disease was overshadowed by its devastating effects in the shipyards on the West Coast which were building Liberty ships. All armies suffer from "athlete's foot" and it looks as if this will be true for a long time. The chief lesson of this essay is that some men never get it and some are never cured, and that footbaths are a waste of time and hypochlorite. The identification of Q fever as the cause of the epidemics of pneumonia-like illness in all the armies in Italy is a good story which might have had more space: the evidence incriminating the accumulated dust in cow byres is strong and accords well with the time-honoured association between typhus and second-hand clothes. The last essay is on viral hepatitis, and it is probably the best history of the disease that has been written. We imagine that even General George Marshall, imperturbable as he was, had some anxious moments when he learned that his soldiers in every theatre of war were turning as yellow as a row of guineas, and that in some places almost half of them were in hospital. It might have been yellow fever. It was not, and the administrative efficiency of the Medical Corps and its civilian advisers was proved to the hilt by this curious accident.

It is in the dull purple of the Medical Corps that this book is bound: a gloomy colour which recalls much professional excellence and good comradeship. The printing is good and many pictures illuminate the text.

1. See *Lancet*, 1959, i, 503.

The Extra Pharmacopœia (Martindale)

Supplement 1961 to vol. II. (23rd ed., 1955) and vol. I. (24th ed., 1958). London: The Pharmaceutical Press. 1961. Pp. 315. 32*s*. 6*d*.

MANY practitioners have given up the struggle of coping with new pharmaceutical preparations. The enlightened doctor keeps volume I of Martindale on his desk, for this book is a mine of information on many important topics; and he will welcome the enterprise of the Pharmaceutical Society of Great Britain in embarking on a series of supplements. This *Supplement* amends information in both volumes of the *Extra Pharmacopœia*; and there is a further list of new drugs and proprietary medicines which, with the Addenda, includes notes on preparations marketed as recently as April, 1961. Many family doctors will be interested in the list of 1000 "counter" proprietaries. It is perhaps a pity that manufacturers' claims on behalf of these products have been omitted from Martindale. The reader must fall back on his own knowledge of clinical pharmacology to assess the therapeutic possibilities in such preparations as Anti Fog Bronchial Lozenges. He might also become aware for the first time of the mental strain imposed on the retail pharmacist whose opinion is sought on the relative merits of Cabdriver's Adult Linctus and Cabdriver's Junior Glucose Linctus.

Hæmophilic Diseases in Denmark

A classification of the clotting defects in 78 *hæmophilic families.*—KNUD-ERIK SJØLIN, M.D., Institute of Human Genetics, University of Copenhagen, and Biological Institute, Carlsberg Foundation, Copenhagen. Oxford: Blackwell Scientific Publications. 1961. Pp. 339. 35*s*.

DENMARK is a country where tracing members of families seems relatively easy and where there is a university Institute of Human Genetics which maintains a medico-genetic register. In 1943 Andreassen published details of 35 hæmophilic Danish families; and Dr. Sjølin has followed up the history of these 35 families and added details of 43 more. Techniques for detecting hæmophilia have completely changed since 1943, and it is now known that the clinical picture of hæmophilia is shared by a number of related syndromes of which Christmas disease accounts for 15–20% and classical hæmophilia for most of the remainder; there are also a few other syndromes, such as Hageman-factor deficiency, that arise only rarely. Dr. Sjølin has sorted out the 148 affected members of these families by up-to-date techniques. The first half of the book deals with the techniques and the results taken together; the second half gives details, including genetic data, of each of the families.

It is perhaps unfortunate that he prefers the thrombin generation test to the more widely used thromboplastin generation test, since this makes his results less readily compared with those of others. The other methods used are quite usual, but no quantitative assays of antihæmophilic-globulin deficiencies have been made. The reassessment of Andreassen's families showed that in 3 families there was no detectable clotting defect, and many others suspected of having rare syndromes were in fact mild cases of hæmophilia or Christmas disease. Nevertheless Sjølin has found 3 cases of Rosenthal's plasma-thromboplastin-antecedent deficiency and 11 of Hageman-factor deficiency; 25 are thought to have combined antihæmophilic-globulin and Christmas-factor deficiency. A particularly full description is given of the methods used for detecting the Hageman-factor deficiency. A surprising finding is that prolonged clotting-times of the blood were detected in 9 out of 10 mothers of sons with typical hæmophilia. This is so different from experience elsewhere as to throw some doubt on the other results of Dr. Sjølin's survey, but the results are given in full so that those interested can go into them in detail.

In spite of some shortcomings in technique, the study is a

valuable addition to detailed knowledge of the best-documented hereditary disease, and all interested in genetics or hæmophilia will wish to read it.

The Analysis of Therapeutic Groups

Institute of Psychiatry Maudsley Monographs no. 8. F. KRÄUPL TAYLOR, M.D., D.P.M., consultant physician, Bethlem Royal Hospital and Maudsley Hospital. London: Oxford University Press. 1961. Pp. 122. 25*s*.

DR. TAYLOR'S approach to psychotherapy in groups may be termed analytic rather in the sociological than in the Freudian dynamic-psychological sense. Indeed, in his opening chapter, he evaluates psychotherapy merely as being "like many other forms of medical and surgical treatment . . . a palliative procedure whose aim is to relieve suffering and allow time for remedial adjustment". Apart from the so-called "Hawthorne effect" of attention to the patient's personality, he considers that psychotherapy owes its curative powers to four procedures: temporary reduction of social restrictions; the confession of sins; emotional excitation; and interpretation of the meaning of illness and symptoms. He explains how these procedures apply in the therapeutic group, and briefly mentions the various methods of group psychotherapy. Dr. Taylor describes his own methods of selection of patients for the group, based on medical and psychiatric examination, and the balancing of habitual talkers and habitual listeners of the same age-group and of each sex. He is explicit about the tasks he expects his groups to perform—candid self-revelation, disclosure of significant life experiences, and a search for interpretations that will make neurotic responses seem intelligible.

The two longest chapters are concerned with a survey of the study of therapeutic groups, and a narrative account of one of Dr. Taylor's groups. The results of treatment and analysis of this group are given in the next chapter. Besides recording the group's topics of discussion and the relative part played by each member, Dr. Taylor assesses the members according to their dominance and popularity. He also asks them to rate themselves and each other for these qualities, both in relation to the whole group and in dyadic interactions. The final chapter summarises his findings, many of which will interest those concerned with groups. Not surprisingly, public dominance proved to be fairly easily assessed by group members, public popularity of colleagues less so, and personal popularity least of all. Patients with a high dominance and low popularity tended to leave the group prematurely on some plausible pretext.

Progress in Clinical Medicine (4th ed. London: J. & A. Churchill. 1961. Pp. 345. 50*s*.).—This new edition of the well-known book edited by Dr. Raymond Daley and Dr. Henry Miller follows the pattern of its predecessors. Advances in various branches of medicine during the past five years are described and critically discussed by twelve experienced authors. The result is an authoritative survey, the more valuable because the contributors are not afraid to express their own opinions, and are at pains to offer critical guidance through the jungles of new fact. A new and fascinating chapter on Space Medicine by Wing-Commander P. Whittingham may well become a permanent feature of future editions. This book is invaluable to general physicians trying to keep up with their registrars, and it is also highly recommended to membership candidates.

Biological Approaches to Cancer Chemotherapy (London: Academic Press. 1961. Pp. 431. 96*s*.).—This volume, edited by Dr. R. J. C. Harris, brings together the papers and discussion at a symposium held in Louvain in June, 1960, under the auspices of UNESCO and W.H.O. The symposium was concerned with the best ways of utilising the available information about the properties of living cells in designing drugs for the treatment of tumours. The editor says that the probability is that all the necessary clues are available, and failure to solve the problem is the result of inadequate intellectual effort. Yet the 31 papers in this symposium give some idea of how intense this effort is. Biochemistry, immunology, and some electron microscopy are the subjects represented. To those working in this subject, most of the material will be familiar, but they may well find it useful to have in one book these varied papers from 38 contributors. The doctor who is treating malignant and allied diseases will be impressed by the immense amount of fundamental work going on, and even if he cannot follow much of it in detail, he will see that the design of new drugs is now anything but haphazard.

Science Survey (2) (London: Vista Books. 1961. Pp. 364. 30*s*.)—The British Association for the Advancement of Science last year sponsored the publication of a collection of articles of general interest, largely based on lectures delivered at its meetings. This *Science Survey* was so well received that a second issue has now been prepared, under the editorship of A. W. Haslett and John St. John, containing some twenty-five papers on such varied topics as the theory of relativity, and jet engines as a nuisance to householders near an airfield. Those on the nature of nerve impulses and on current problems in psychological research will particularly appeal to medical readers.

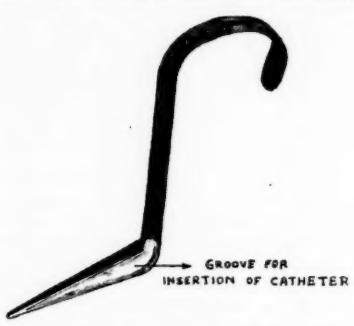
Virus and Rickettsial Diseases of Man (3rd ed. London: Edward Arnold. 1961. Pp. 461. 60*s*.).—This excellent book, by Sir Samuel Bedson, Prof. A. W. Downie, Dr. F. O. MacCallum, and Prof. C. H. Stuart-Harris, has been substantially changed for this new edition and provides a thoroughly up-to-date account. It will be especially valuable to clinicians and medical students, notably because it explains clearly the help the laboratory can give in diagnostic problems. The descriptions of the individual diseases are lucid and well written, with special emphasis on pathology and epidemiology, means of diagnosis, and control.

New Inventions

A SIMPLE CARDIAC CATHETER INTRODUCER

NOT infrequently one has difficulty in introducing a cardiac catheter into a vein, even after a fish-mouth opening is made. The introducer shown in the figure has greatly facilitated the procedure in my hands.

The instrument is L-shaped, with the short limb, which is



about $^{3}/_{4}$ in. long, tapered to a blunt point and grooved underneath. The other end of the long limb is curved.

After a slit is made in the vein, the pointed end is gently introduced, and the short limb is pushed as far as it will go. The long limb of the instrument is held up vertically with the left hand, and the catheter tip is introduced along the groove underneath the short limb into the vein. Once the tip is inside the vein, the instrument can be withdrawn.

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THE LANCET

LONDON 21 OCTOBER 1961

Scientific Manpower—and Medicine

THE Committee on Scientific Manpower,[1] though very cautious about the basis of its estimates, gives definite and helpful figures, first on the future supply of scientists and technologists, and secondly on the future demand for their services. The total annual output of scientists and technologists is expected to rise from about 14,300 in 1959 to about 27,500 in 1970, and the total demand from 173,000 in 1959 to 328,500 in 1970. Those employed in industry, who constituted about 44% in 1959, may amount to about 50% by 1970, while there is likely to be a corresponding fall in the proportion employed by the Government and the public corporations. There will, however, be a falling annual rate of increase in scientific manpower employed by Government and private industry, whereas in the public corporations and education the rate of increase will probably rise. A point of interest is that, whereas by 1965 scientific manpower will roughly balance demand, there will actually be a shortage of technologists offset by an excess of scientists. By 1970, it is thought, there will be an excess of both scientists and technologists.

The committee, over which Sir SOLLY ZUCKERMAN presided, does not give corresponding figures for the medical profession; but it notes that in 1959 the full-time students preparing for qualifications in medicine (human and veterinary), dentistry, and agriculture were about 19,000 and in 1970 the estimated figure is 21,000. On the committee's estimate there may, it seems, be a big transfer of manpower from medicine into science and technology; and this could seriously damage our profession, by depriving it of its fair share of good minds.

Obviously it is right to try to forecast future requirements for all sorts of manpower which need a long period of education, and to try to fill expected deficiencies. And the need for doctors should certainly not be ignored. But it would be a mistake to suppose that doctors are recruited wholly from the scientifically minded, or that competition for the best brains lies exclusively between medicine and science. Medical students compete with science in that they need places in the scientific side of education; but there are motives other than scientific interest which lead a man to spend a lifetime in medicine, and the medical profession does not draw from exactly the same field of interest as the scientific and technological professions. It is all too easy to say that the National Health Service is responsible for providing the incentive—that if the pay is made adequate there will be plenty of doctors. But in point of fact the motives which determine entry into medicine or any other profession are not as clear as they may appear. Probably only a minority of the young think first about the monetary outlook: they may be influenced more by the mental image of "the doctor". This image can change considerably over the years, and there is no doubt that it has lost status in the last half-century—partly because of the behaviour of a small but conspicuous minority of the profession after the introduction of the National Health Service and partly because increase in knowledge about medicine among the lay public has diminished the feeling that doctors, individually, are men of mystery and power. The doctor portrayed by LUKE FILDES—a noble, determined, learned, strong, resourceful, gentle, and unselfish figure—is sometimes derided by the young today; but as an ideal he did attract the best, and he would still do so if people still believed that doctors were like that. One still meets young doctors who admit that they went into the profession as a result of admiration of a particular doctor. In other words, although it is easy to put the responsibility on the authorities, the raising of the status of the profession is not entirely a thing for "them" to do. "They" might retort that it is within the power of every doctor who comes in contact with laymen to influence the public in the right direction. The medical profession is to no small extent responsible for its own future.

1. The Long-term Demand for Scientific Manpower. Advisory Council on Scientific Policy: Committee on Scientific Manpower. Cmnd. 1490, 1961. H.M. Stationery Office. Pp. 26. 1s. 9d.

The Meliturias

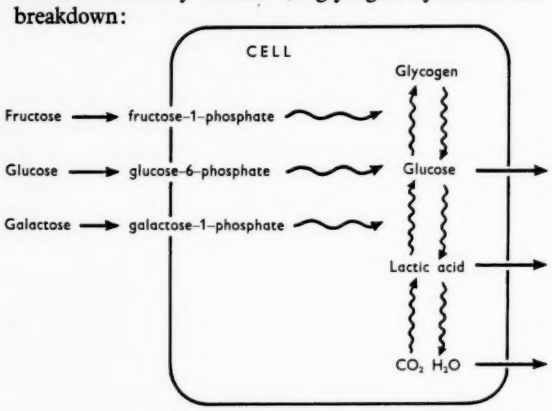
WHEN THOMAS WILLIS tasted the urine of a diabetic in 1666 and found it sweet he might have forestalled terminological confusion by describing the condition as "melituria". In three hundred years the term would have no doubt acquired an air of venerable quaintness: instead it has now been attached to a group of metabolic disorders which do not include the two commonest examples of "honeyed" urine—diabetes mellitus and renal glycosuria—but which do include at least one condition in which the urine contains sugar but does not taste sweet and possibly another in which it smells like syrup but contains no sugar. Biochemically the meliturias have little in common; and in clinical practice, while they are probably all genetically determined and all have at one time or another been mistaken for diabetes mellitus, they vary from harmless curiosities to usually fatal diseases.

Among the meliturias, familial pentosuria may be accorded first place, not because of its clinical importance (which is slight), but as one of the original quartet of "inborn errors of metabolism". GARROD noted that it tends to crop up in more than one member of a family, that it is detectable by chemical tests at birth, and that it causes no symptoms [1]; and fifty years later there is little we can add to his observations. Unlike the mixed bag of five-carbon sugars which are some-

1. Garrod, A. E. Inborn Errors of Metabolism. London, 1923.

times excreted normally in urine after a meal, the pentose of familial pentosuria is pure *l*-ketoxylose.[2] Its source is not the gut (at least not directly) but the body pool of carbohydrate residues from which it is synthethised along abnormal and as yet obscure enzymatic pathways. In its biochemical origin it is therefore more akin to the uricaciduria of gout or the cystinuria of cystinosis than to the other meliturias.

The two hexoses, or six-carbon sugars, which are the characteristic urinary finding in at least three distinct meliturias are fructose and galactose. Structurally these both resemble glucose (galactose differs from glucose only in its spatial configuration) and the normal organism deals with them along closely parallel lines. All three sugars enter the cell by being converted to phosphate esters by their respective phosphorylating enzymes—hexokinase for glucose, galactokinase for galactose, and fructokinase for fructose. Phosphorylation not only permits their passage across the cell membrane but also provides them with the energy necessary to pursue their intracellular metabolic courses. These consist in a series of linked transformations which lead them to a common metabolic pool—or, more accurately, into a common two-way stream of glycogen synthesis and breakdown:



In essential fructosuria fructose is probably imperfectly phosphorylated and therefore never enters the cell—at least not in bulk.[3 4] Apart from a largely theoretical loss to the body's carbohydrate economy (after glucose, fructose is the most important monosaccharide constituent of food), this has no ill-effects. The blood-fructose rarely rises to very high levels since it is rapidly excreted by the kidneys; and the only risk to the patient is that at an insurance examination the disorder may be mistaken for mild diabetes.

The other two hexose meliturias—fructose intolerance and galactosæmia—differ from essential fructosuria both in their chemical mechanism and in their clinical effects. Fructose in fructose intolerance and galactose in galactosæmia have no initial difficulty in traversing the cell membrane; and they enter on their intermediate metabolism in the normal way. At some stage, however, the chain of transformation which should lead them to the glycogen-glucose two-way stream is broken by the absence of an essential enzyme link—P-gal-uridyl-transferase in the case of galactosæmia and (probably) 1-phosphofructaldolase in the case of fructose intolerance.[5–8] Pressure from behind leads to the accumulation of the "proximal" intermediate metabolite; and the result, in DALGLEISH's telling analogy, is not unlike a major traffic block in a congested city:

"The streets (which can be likened to intracellular chemical pathways) absorb, within limits, variations in traffic flow. If it is necessary to close one street for repair, the traffic can be diverted; and the overall pattern of traffic entering and leaving the city is affected only slightly. However, if a major blockage occurs, such as the closing of an only bridge across the river, the pattern changes drastically".[9]

The staggering number of chemical reactions which take place in every cell simultaneously and yet without interfering with each other depend on the selective affinity of every enzyme for its specific substrate; but this affinity, however strong and specific, is only relative. In other words, when an intermediate metabolite accumulates and reaches very high concentrations, it will, by sheer bulk, begin to combine with (and in this way immobilise) enzymes to which its normal affinity is low. In galactosæmia galactokinase, and in fructose intolerance fructokinase, are thus inhibited comparatively early; and, since these enzymes are essential for the entry of their respective substrates into the cell, the inhibition leads to a secondary rise in extracellular blood-galactose or blood-fructose. More serious is the secondary inhibition of enzyme pathways inside the cell. One which has been recognised only in recent years involves the breakdown of glycogen and is therefore essential for the maintenance of a normal blood-glucose level.[10 11]

When a galactosæmic infant is given a milk feed (which, on hydrolysis in the gut, yields both glucose and galactose), the clinical ill-effects and the accumulation of galactose phosphate in the tissues are reflected in two dramatic changes in the bloodchemistry: the blood-galactose rises often to very high levels and, almost at the same time, the blood-glucose falls.[12] In fructose intolerance a similar fall accompanies the rise in blood-fructose.[6 8] In either condition the blood-glucose effect may not be apparent when only the total blood-sugar is estimated by non-enzymatic methods; and until a few years ago even profound hypoglycæmia used to go unrecognised. It is possible, moreover, that in an attempt to maintain a normal blood-*sugar* level, homœstatic mechanisms further depress the already falling blood-glucose. It is not yet clear to what extent such repeated hypoglycæmic episodes, rather than toxic intermediate metabolites of galactose and fructose, must be held responsible for the damage to brain, liver, and

2 Marble, A. *Med. Clin. N. Amer.* 1947, **31**, 313.
3. Hers, H. G. Le métabolisme du fructose. Brussels, 1957.
4. Leuthardt, F. Kolloquium der Gesellschaft für Physiologische Chemie. Berlin, 1958.
5. Isselbacher, K. J. *J. clin. Lab. Med.* 1957, **36**, 902.
6. Froesh, E. R., Prader, A., Labhart, A., Stuber, H. W., Wolf, H. P. *Schweiz. med. Wschr.* 1957, **87**, 1168.
7. Hers, H. G. *Chem. Weekbl.* 1961, **57**, 431.
8. Dormandy, T. L., Porter, R. J. *Lancet*, 1961, i, 1189.
9. Dalgleish, C. E. *in* Scientific Basis of Medicine Annual Reviews; p. 129. London, 1961.
10. Sidbury, J. B. *Abstr. Pap. Amer. chem. Soc.* 1957, **132**, 27C.
11. Wolf, H. P., Leuthardt, F. *Helvet. chim. Acta* 1957, **40**, 1027.
12. Komrower, G. M., Schwarz, V., Holzel, A., Goldberg, L. *Arch. Dis. Childh.* 1956, **31**, 254.

other tissues which are the permanent legacy of delayed diagnosis; but brain-cells are particularly sensitive to glucose lack, and many acute neurological manifestations —convulsions, coma, even sudden death in infants—are almost certainly hypoglycæmic in origin. The very high blood-fructose and blood-galactose levels which have been recorded in fructose intolerance and in galactosæmia respectively probably reflect the development of a secondary renal threshold for those sugars—an obscure mechanism which may be analogous to the rise in glucose threshold sometimes found in diabetes. Familial fructose and galactose intolerance have features in common both with fructose intolerance and with galactosæmia.[8]

Of the disaccharides which are occasionally detected in the urine, maltose (2 glucose units) is the least common and probably the least important and lactose (1 glucose and 1 galactose unit) the most common but also the most physiological. The lactating breast is the one normal site where non-glucose sugars are elaborated from glucose; and in late pregnancy, some degree of lactosuria and galactosuria is the rule rather than the exception. The role (and possible dangers) of these milk-sugars in newborn and especially in premature infants is still disputed.[13] Even more controversial is the significance of the third urinary disaccharide—sucrose—whose two hexose units (1 glucose and 1 fructose), joined together by their reducing groupings, do not give a positive reaction with the usual copper reagents. In a sense, therefore, sucrosuria has been a revelation of the age of clinical chromatography; and it was not until 1954 that MONCRIEFF and WILKINSON [14] first described a syndrome of mental retardation and hiatus hernia which, they suggested, was associated with a defect in sucrose metabolism. Before sucrose (or any other dietary disaccharide) can be excreted in the urine it must escape hydrolysis in the gut, and for this reason sucrosuria is never a normal finding; but that it constitutes a biochemical and clinical entity comparable to galactosæmia or fructose intolerance is now in serious doubt. In infancy and childhood sucrose is often found in the urine; and, especially during acute gastrointestinal illness, it can certainly reach high concentrations.[13 15]

If melituria is accepted as having any meaning at all, "maple-syrup-urine disease" ought to be included in the group. (Our methods have changed since the days of WILLIS; and, while the odour of maple-syrup urine is inescapable, published reports make no reference to its taste.) This fascinating metabolic error differs from other meliturias in being a disorder not of carbohydrate but of aminoacid metabolism.[16–18] The maple-syrup smell probably emanates from α-oxoisocaproic acid—a ketoacid derived leucine, one of three aminoacids whose metabolism is grossly disturbed. Clinically the condition is associated with progressive cerebral degeneration and (in all cases so far reported) death in infancy; biochemically the site of the primary metabolic block is still being investigated. Like that of many other inborn errors of metabolism, its mechanism may well shed new light on some of the fundamental biochemical processes of the normal organism.

13. Haworth, J. C. *ibid.* 1960, **35**, 552.
14. Moncrieff, A., Wilkinson, H. R. *Acta paediat., Uppsala.* 1954, **43**, suppl. 100, p. 495.
15. Perry, T. L., Lippman, R. W., Walker, D., Shaw, K. N. F. *Pediatrics*, 1959, **24**, 774.
16. Menkes, J. H., Hurst, P. L., Craig, J. M. *ibid.* 1954, **14**, 462
17. Dancis, J., Levitz, M., Miller, S., Westall, R. G. *Brit. med. J.* 1959, i, 91
18. Dent, C. E., Westall, R. G. *Arch. Dis. Childh.* 1961, **36**, 259, 269

Time in the Machine

To the specialist it sometimes seems as if patients are referred urgently to him more for dramatic or social reasons than because of a need for his intervention, whereas on the other hand patients whom he would gladly see and treat at once take an unconscionable time a-coming through the preliminary screening. Thus the neurosurgeon may be asked to see an elderly patient with a vascular catastrophe within a few hours of the onset, whereas he may find that a man in his thirties reaches the special unit a week after the onset of complete paraplegia and a full six months after the onset of progressive symptoms. Six months hardly represents the period that a time-and-motion expert would regard as satisfactory, but human beings are not factory pressings. The patient himself may not complain of what seems a trivial symptom or may be unwilling to accede to the first suggestion that he should see a surgeon who may propose an operation on his head or spine; and the existence of waiting-lists for certain types of case may engender a sense of apathy.

SEGELOV and DAVIS [1] have analysed the clinical data on 700 verified cases of cerebral tumour admitted to the neurosurgical department of the Royal Prince Alfred Hospital, Sydney. In cases of meningioma, as in all the others, there was a long delay between the first symptom and diagnosis. About a quarter of these patients presented with epilepsy, starting in adult life and commonly focal; nearly all had other clinical features before they were admitted to hospital, and half of them had papilloedema by that time. Those with the classical features of raised intracranial pressure—headache, vomiting, and papilloedema—were referred to hospital more quickly, but the results of surgical treatment were not so favourable in these as in others. Patients with pituitary tumours or craniopharyngiomas usually presented with visual defect, raised intracranial pressure, epilepsy, mental deterioration, or other neurological defect. In only a quarter of the cases did the illness begin with overt endocrine disorder. Half the patients had experienced symptoms for over two years before admission, and a further quarter for over five years. Results of treatment were incomparably better in the group diagnosed early.

Acoustic neurilemmoma might begin with unilateral deafness, and three-quarters of these patients had had symptoms for two to ten years before admission; or with ataxia and giddiness, and half this group had had symptoms longer than two years. In patients who had had symptoms for less than two years the mortality was nil: in the others it was 45%. (The picture regarding gliomas was similar. Diagnosis was especially late when the disease began with epilepsy.) There is no reason to

1. Segelov, J. N., Davis, R. *Med. J. Aust.* 1961, ii, 1.

believe that other centres are immune to similar difficulties. Appealing for early diagnosis in acoustic neurilemmomas McKissock [2] reported that, of 270 cases dealt with between 1940 and 1960, only 8 were diagnosed at an early stage when the tumours were less than 3 cm. in diameter. These were diagnosed from partial deafness, confirmed by otological tests, and were removed without fatality. Of these early cases 6 had fifth-nerve involvement, and 1 seventh-nerve impairment. Air studies confirmed the diagnosis in 1 case and were normal in 7. The internal meatus was radiologically enlarged in 2 cases. In 2 out of 5 tested, the protein in the cerebrospinal fluid was increased. At operation the tumour could be separated from the eighth nerve by a blunt hook. In 5 cases eighth-nerve function was preserved; in 3 of these no increase in the preoperative degree of deafness ensued. In the remaining 3 the nerve was macroscopically intact but the hearing was lost. Several had transient seventh-nerve weakness but all recovered in a few weeks or months. McKissock concluded that early diagnosis should be sought by means of otological tests: the diagnosis is confirmed by finding nerve deafness without evidence of recruitment on audiometry, and diminished response to caloric stimulation.

It is true that the tempo of neurosurgical units is measured and that outpatients may wait for an appointment (and also that half the patients are at present untreatable by any means). But two years' average interval between onset and special investigation is in a different time-scale of procrastination. Even now, thirty-five years after modern neurosurgical methods were instituted in this country, the neurosurgical specialty may still lack the full confidence of the public or the profession. Or is the neurosurgeon right when he says that early symptoms and signs are not known as well as they might be—such symptoms as epilepsy (especially focal) starting in adult life, unilateral deafness, or multiple neurological defects of insidious onset and progressive course? Two years—this is not really very satisfactory. The only remedy is for everyone from patient to specialist to be mindful of the possible significance of the first symptom.

2. McKissock, W. Proceedings of the Society of British Neurological Surgeons, 63rd meeting. *J. Neurol. Neurosurg. Psychiat.* (in the press.)

Annotations

A PHARMACEUTICAL CRISIS

SINCE 1948 until last July neither the public nor the cognate professions had heard much of the pharmacists' payments from the National Health Service; and, indeed, some misapprehensions had sprung from Parliamentary and other criticisms of the "drug bill". Three months ago it was stated by the Central N.H.S. (Chemist Contractors) Committee, which constitutes the staff side of the Whitley Council for Retail Pharmacy, that chemists, including the company and cooperative shops, might withdraw in mass from the N.H.S. if negotiations with the Ministry of Health broke down. Now the committee announce that suggestions from the Ministry on future remuneration are unpalatable and unacceptable; and after a representative body has considered the proposed terms it seems almost certain that chemists will give the three months' notice required for their withdrawal from the pharmaceutical service.

Not only are the proposed terms said to be unacceptable, but a matter of principle is also at stake. The Ministry has always regarded payments to chemists as an overall figure, although it consists of two factors—a dispensing fee (at present 14·57*d.* per average prescription) and an "on-cost" of 25% of the wholesale value of the medicaments or appliances dispensed; when the Service began, this second figure was 30%, but it was cut to 25% ten years ago. Pharmaceutical opinion has been hardening steadily in favour of dissociation of these two factors, and earlier this year pharmacists lodged a claim for a professional fee to yield an average of 2*s.* per prescription with the on-cost maintained at 25%. Since the present settlement was reached, based on 1956 figures, there has been a continuous rise in ingredient values and consequently gross "on-cost" has been higher than forecast by the Ministry's statisticians. They believed, as Sir Bruce Fraser told the Committee for Public Accounts, that chemists would receive a net profit of $2^1/_4$*d.* per prescription after all expenses had been met, but this turned out to be close to 4*d.* in 1957. The present offer, according to the Ministry estimates, would show about $4^1/_2$*d.*, and is, in the official view, just, reasonable, and indeed generous, although it is admitted contractors' expenses have been rising also. The dispensing fee would be raised to over 17*d.* per prescription, but the overall figure for "on-cost" would be brought down to 18% by introducing differential payments. The "on-cost" on the first 500 prescriptions dispensed each month would remain at 25%, but for the next 250 it would be 20%, and for the remainder only $12^1/_2$%.

In the course of the negotiations, many complicated inquiries into working costs, container costs, and actual buying prices of drugs have been undertaken; and the interpretations of the results have shown wide differences in opinion between the Ministry and the profession's accountants and statisticians. The present difference, however, is wider and more fundamental. Pharmacists believe that their educational standards and their professional skill merit recognition by a proper professional fee, and they regard calculations based on tenths or hundredths of a penny as insulting and derisory. Whatever may happen, it is certain that pharmacists will try to minimise hardship to the public, though if they withdraw, medicines may be available only on a "cash-and-carry" basis.

EXTRAPYRAMIDAL EFFECTS OF TRANQUILLISERS

THE tranquillising drugs tend to give rise to extrapyramidal disturbances. Indeed, some workers regard the onset of an extrapyramidal syndrome as indicating a therapeutic level of action; but, as we mentioned with reference to thioproperazine,[1] this has not yet been proved. The syndrome is generally thought to be completely reversible: irreversibility has been reported in some older patients,[2] but "in such cases it is difficult to separate drug effects from the degenerative processes of aging".[3]

1. *Lancet*, Sept. 23, 1961, p. 698.
2. Uhrbrand, L., Faurbye, A. *Psychopharmacologica*, 1960, **1**, 408.
3. McGeer, P. L., Boulding, J. E., Gibson, W. C., Foulkes, R. G. *J. Amer. med. Ass.* 1961, **177**, 665.

Ayd [4] has reviewed 3775 cases treated with tranquillisers, excluding patients who had received only the weaker drugs, such as mepazine or preomazine, since these rarely cause extrapyramidal reactions. Of the total, 47·8% of the women and 29·6% of the men had such reactions, and this difference was present in almost every age-group. There was also a sex difference in the type of reaction—restlessness and parkinsonism were twice as common in women, whereas dyskinesia was twice as common in men. Ayd relates both clinical potency and frequency of extrapyramidal reactions to the chemical structure of the drugs. Least potent is the group with a piperidine ring in the side-chain (e.g., mepazine); next is the chlorpromazine-type group, with a 3-carbon straight side-chain—in large doses these may cause reactions. The piperazine group (e.g., trifluoperazine) is the most potent, and extrapyramidal reactions may be expected when they are used. Other differences are correlated with the configuration of the side-chain (perphenazine causes relatively fewer reactions than prochlorperazine) and with the halogen attached to the nucleus: thus, substitution of the trifluoromethyl halogen for chlorine, as in trifluoperazine, gives a much higher incidence. Chemical structure is also related to the type of extrapyramidal reaction. What emerges, most surprisingly, from this analysis is that personal predisposition had more influence than any other factor—whether duration of treatment or the chemical structure, relative potency, or dosage of the drug. Thus, 61% of the total group had no neurological reaction at all, though they took the same drugs, in equal doses and for equal lengths of time, as the affected patients.

McGeer et al.[3] point out that the action of tranquillisers may be linked to interference with the central action of aromatic amines—particularly serotonin or the catecholamines. The rauwolfia alkaloids deplete the brain of both, by competing for their binding sites, while the phenothiazines block their action after release. Clinically, the results are tranquillisation and sometimes the extrapyramidal syndrome, though it is far from proven that clinically these actions are mediated through this particular chemical mechanism.

The fact that dopamine is found in highest concentration in the corpus striatum led Carlsson [5] to suggest that the extrapyramidal effects of reserpine might be due to depletion of this amine. Its precursor (dihydrophenylalanine or dopa) will counteract many of the effects of reserpine, and experimentally it has a powerful neuroinhibitory action. McGeer et al. suggest that the phenothiazines may also produce their extrapyramidal effects by interfering with the action of dopamine, and that this may result in the emergence of a competitive neurotransmittor system involving acetylcholine and histamine (antiparkinsonian drugs are either anticholinergic or antihistaminic, or both). They attempted to test this hypothesis by giving dopa to patients with extrapyramidal reactions, induced by reserpine and one of three phenothiazine drugs. Dopa was effective only in some mild cases, and then not completely; on the other hand, diphenhydramine hydrochloride controlled the reactions in every case. Although these results do not support the suggestion that interference with the action of brain catecholamines is a primary disturbance, McGeer et al. claim that this is not disproved since we have no way of knowing whether the levels of brain catecholamines were affected at all.

4. Ayd, F. J. *J. Amer. med. Ass.* 1961, **175**, 1054.
5. Carlsson, A. *Pharmacol. Rev.* 1959, **11**, 548.

McGeer et al. conclude with some interesting observations on the action of histamine. The effectiveness of some anti-histamines against parkinsonism has usually been attributed to some undiscovered property, unrelated to their main action. Yet phenothiazines that are relatively strong anti-histamines, such as promethazine hydrochloride and chlorpromazine, are much less likely to produce extrapyramidal reactions than weakly antihistaminic ones (e.g., trifluoperazine). Histamine is antagonistic to catecholamines on many peripheral smooth-muscle preparations, and if this applied also in the central nervous system, histamine might be involved in extrapyramidal function. Possibly a theoretical break-through in connection with drug-induced parkinsonism would lead to effective control of this whole syndrome.

FRACTURES OF THE CARPAL SCAPHOID

ALTHOUGH fractures of the carpal scaphoid have been recognised for many years it was only during the 1939–45 war that their real importance became apparent. At that time there were large numbers of young men in the Forces playing games, undergoing physical training, or engaged in assault courses. In such activities falls on the outstretched hand are inevitable, and large numbers of fractured scaphoids were discovered. It was important to establish the best treatment, since a persistent disability often led to discharge from the Service and a pension.

At the beginning of the war prolonged, continuous, and extensive immobilisation [1] was the standard treatment. This led to bony union in the majority of cases; but it often necessitated a long period of "light duty", and even after several months in plaster the patient sometimes complained of persistent pain and stiffness. A little later, bone-grafting was advocated.[2] Then, after the war, some surgeons—chiefly those who worked with pensioners—recommended such procedures as excision of the scaphoid [3] excision of the radial styloid, or even excision of the proximal row of the carpus and, at a later date, plastic replacement of the scaphoid to relieve pain. In some patients arthrodesis of the wrist was performed. Of these procedures, excision of the radial styloid was on the whole the most successful when pain persisted and the fracture was ununited; but in general the results were seldom completely satisfactory.[4]

Most surgeons are aware that some patients in whom fracture of the scaphoid has not been diagnosed or treated may nevertheless have excellent function. London,[5] of the Birmingham Accident Hospital, advocates symptomatic treatment—namely, only six to eight weeks in plaster. At the end of this time, provided the wrist is comfortable, and whatever the radiograph shows, the patient is allowed to use his wrist freely. In other words the patient, not the radiograph, is treated. In some 50 of his 300 recent cases there was no union radiologically for at least three months after fracture, and in some cases twelve months or more elapsed before bony union took place; and union took place even though the wrist was in active use and was unprotected. Two-thirds of the 300 patients were in plaster for two months or less, and only a tenth for more than three months; and most returned to work within a month of having the plaster removed. Similarly, in treating 60 old ununited fractures with

1. Watson-Jones, R. *Brit. med. J.* 1934, i, 937.
2. Armstrong, J. R. *Lancet*, 1941, i, 537.
3. Dwyer, F. C. *J. Bone Jt. Surg.* 1949, **31B**, 572.
4. Thomas, G. E. *ibid.* p. 134.
5. London, P. S. *ibid.* 1961, **43B**, 237.

secondary arthritis London merely puts the wrist in plaster for three weeks until the effects of the acute sprain have passed off. In his experience it is seldom necessary to perform an arthrodesis of the wrist.

At the Birmingham Accident Hospital about a hundred new cases of fractured scaphoid are seen each year; the population at risk is estimated at roughly a quarter of a million. Clearly, therefore, a large number of people fracture their scaphoid each year; and, as they are mainly young healthy men, the economic loss must be considerable. Any improvement in treatment which reduces the time off work is of value.[6] In many ways London's method is revolutionary, but in other respects it represents a return to the practice of thirty years ago. His report is likely to stimulate many to ask whether they have accepted current orthodox teaching too uncritically.

HIATAL REPAIR

IN the past decade some may reasonably have doubted the efficacy of surgical treatment for hiatus hernia. All too often patients have returned with recurrence or persistence of reflux; and, though this has not invariably been associated with recrudescence of symptoms, failure to produce competence at the cardia can hardly be regarded with satisfaction. Collis's account [7] of the results in a surgical series is therefore of particular interest.

Commonly the hiatus has been closed behind the œsophagus. In the light of anatomical investigations of the diaphragm and manometric studies undertaken in isolated stomachs, Collis et al.[8] concluded, as had Barrett,[9] that an important factor in maintaining competence at the cardia is the acuity of the angle between œsophagus and stomach. This conclusion is now reinforced by Greenan,[10] who conducted manometric studies on 15 patients at laparotomy under general anæsthesia. Collis has based surgical repair of the hiatus on this conclusion, closing the gap *in front of* the œsophagus; by pushing the œsophagus backwards this has had the dual effect of sharpening the cardio-œsophageal angle and of causing the œsophagus to pass more obliquely through the right crus of the diaphragm, thus reducing any tendency of excessive stitching to make the hiatus too small—dysphagia from this cause is a not uncommon immediate sequel of posterior closure. 200 cases were treated thus in the seven years from 1953 to 1960; in 86% the hernia was of the sliding type, and in the rest para-œsophageal; there were only 4 deaths, although 162 patients were aged 40–70 and 10 were over 70. The condition was reassessed radiologically in all patients at one and four years. Both surgeon and radiologist were present when barium swallow was undertaken; stringent measures were taken to induce reflux, such as rolling the patient from side to side while he coughed, and applying abdominal pressure while the patient raised the legs and coughed. Johnstone's acceptance of one reflux as normal [11] was followed in this series only if the amount refluxed was very small. In a follow-up from which there were no omissions, 82 cases were reviewed after four years; reflux was absent or slight in 73 (91%) at one year, and in 60 (75%) at four years; symptomatically the results remained good in 80% at both one and four years (66 and 64 patients respectively). Since 1 patient died within one year of operation and 3 more within four years, the results are slightly better than percentages would lead one to suppose. These results should dispel any doubts as to the efficacy of surgery in experienced hands.

It is a pity that a similar follow-up study of the appreciable number of cases treated by posterior suture has not been recorded for direct comparison. One difficulty in such comparison would be that anterior suture cannot be undertaken in patients with short œsophagus; for this places the hiatus, and therefore the fulcrum around which the œsophagus angulates, at least 3 cm. lower than posterior closure. In order to overcome this difficulty Collis has treated patients with short œsophagus as a separate group. Of 32 such cases in the five years from 1955 to 1960, he has reviewed 30.[12] The œsophagus was prolonged by the addition of a gastric element fashioned from the fundus of the stomach so that anterior hiatal closure could be achieved. The complexity of the original manifestations, which included hæmatemesis and stricture from ulceration, has created difficulty in assessing the relief obtained. A year after operation only 13 patients had good (though incomplete) control of reflux, observed radiologically; but symptomatically the result was excellent or good in 20.

BEING POSITIVE ABOUT DISABILITY

AT the annual congress of the Chartered Society of Physiotherapy last month, both the founders' lecture by Sir John Charles, and a lecture by Dr. David Rice, had as their subject the Whole Man. This emphasis on the need to think of patients as people rather than as bodies, physical signs, symptoms, or potential operations was also the background of a lecture on the Assessment of Disability by Prof. Ruth Bowden. In such assessment, as she said, even purely physical limitations cannot be considered apart from the whole man and his environment. Accurate assessment should be one of the most important means of preventing defeatism, and it should be achieved without inducing pessimism or narrowing the prospects before the patient. The aim is not (as has sometimes been supposed) to compile a catalogue of deficiencies or to concentrate on the extent of the incapacity, but to emphasise what *can* be done.

In considering practical tests of function with reference to the problems of compensation and rehabilitation, Professor Bowden spoke of the importance of accurate prognosis, and showed how patients are sometimes discouraged from returning to work for fear of jeopardising their chances of compensation. She cited the case of a boy with an injured arm whose useful functional recovery was gravely impaired because, on the advice of his lawyer, he did not use the arm for three years. Such cases show the need for understanding of these matters on both sides of industry, as well as among doctors, lawyers, and patients. Though the last twenty years have seen some improvement there is still resistance to an early return to work, and to temporary changes to lighter and more suitable employment. The feeling that it is unfair and unkind to make a recently injured or convalescent man return to work is understandable but often hinders the best recovery. For disability cannot be calculated only in terms of physical incapacity, and everyone concerned should try to provide every incentive to recovery.

6. Watson-Jones, R. Fractures and Joint Injuries; p. 610. Edinburgh, 1955.
7. Collis, J. L. *Thorax*, 1961, **16**, 114.
8. Collis, J. L., Kelly, T. D., Wiley, A. M. *ibid.* 1954, **9**, 175.
9. Barrett, N. R. *Proc. R. Soc. Med.* 1952, **45**, 279.
10. Greenan, J. *Brit. J. Anæsth.* 1961, **33**, 432.
11. Johnstone, A. S. *Brit. J. Radiol.* 1955, **28**, 229.
12. Collis, J. L. *Thorax*, 1961, **16**, 197.

Special Articles

THE ROLE OF THE CARRIER IN STAPHYLOCOCCAL DISEASE

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A GREAT deal has been written about staphylococcal carriers; but most of the articles describe bacteriological studies and are not readily digestible by clinicians. For several reasons, conclusions are apt to be indefinite and recommendations cautious, so that the clinicians and nurses who are ultimately responsible for any action tend to remain apathetic, or frankly cynical. One still meets surgeons who are afraid to face the problem, lest they should be prevented from operating, and most anæsthetists go right through a casualty "list" without washing their hands.

My purpose here is to summarise the evidence and suggest where treatment is likely to prove practicable and fruitful, even without bacteriological control.

TRUE SOURCES OF STAPHYLOCOCCAL SPREAD

The only true sources of staphylococci are septic lesions and carriage sites. These are the places where the organisms multiply. In theory, if we could cut off these sources completely there would be no need to pay any attention to the reservoirs and vehicles for infection—blankets, clothes, ward dust, and so on. Unfortunately, fresh septic lesions and carriers are continually being introduced into hospitals, and their absolute control is impossible. Nevertheless, much can be done.

With regard to septic lesions, clinicians are now well aware of the dangers of septic dermatitis, boils, and infected wounds; but the enormous possible output of staphylococci by patients with staphylococcal bronchitis, enteritis, and urinary infection is perhaps not fully appreciated. That these organisms are pathogenic is obvious from their producing disease; no bacteriological typing is required for confirmation of the fact, and preventive action should be taken without waiting for laboratory reports.

IMPORTANCE OF STAPHYLOCOCCAL CARRIER

It is now well known that in most hospitals well over half the staff carry staphylococci which proliferate in the follicles and glands just inside the nostril, and that many of these organisms are resistant to antibiotics. Of 100 nurses, about 20 never carry; a similar number are persistent carriers; and the remainder carry only for days or weeks at a time. Fortunately very few carriers seem to be dangerous, and in any given outbreak of infection very few (sometimes none) of the nurses and patients are found to be carrying the causative strain.

Some investigators have been led by this to conclude that carriers are relatively unimportant; but this conclusion is unjustified, as is shown from time to time by the incrimination of a single carrier as the cause of an outbreak. The explanation may perhaps be found in the works of Duguid and Wallace (1948) and Hare and Thomas (1956) who have shown that some carriers are heavy dispersers of staphylococci from their clothes, and can scatter staphylococci all over a room simply by walking through it. Such "disperser carriers" are uncommon but it is easy to imagine the damage even one of them could do if he happened to be carrying a really virulent strain.

Hare and Ridley (1958) and Ridley (1959) also pointed to the importance of the perineum as a carrier site. The social difficulties of detecting perineal carriers are such that accurate information is hard to get; and some of the "epidemics" of cross-infection whose cause has defied discovery may have been due to unknown perineal carriers in whom nasal swabs were negative. We are still not certain what part the perineal carrier plays; but probably he or she contaminates the clothes more heavily and is therefore more likely to be a disperser of staphylococci. What is badly needed is a simple test for the dispersion of organisms to replace swabbing of noses and skin sites. As Kinmonth et al. (1958) pointed out, it is the disperser who may be the menace; we are not interested in the healthy carrier who keeps his organisms to himself!

CARRIERS AMONG HOSPITAL STAFF

As already mentioned, the proportion of hospital staff carrying dangerous strains of staphylococci is usually very small, even during epidemics; and the bacteriologist may not be able to pick out the dangerous carriers with certainty, since organisms apparently of a single phage-type may produce havoc in one hospital yet no lesions in another. Nevertheless, some organisms are notoriously pathogenic and should not be ignored. In the absence of bacteriological facilities, clinicians should remember that people with staphylococcal lesions are nearly always nasal carriers of the same strain (Hobbs et al. 1947, Valentine and Hall-Smith 1952, Tulloch 1954, Roodyn 1954, Gould 1955, Gould and Cruickshank 1957) and often perineal carriers as well (Tulloch et al. 1960). Moreover they may continue to carry for months after recovery, despite vigorous antibiotic therapy given systematically for the lesion. Such people may be an even greater menace than we think. Knights (1961), after investigating fourteen explosive outbreaks of staphylococcal sepsis in New Zealand hospitals, found convincing evidence that each had started from a person with a staphylococcal lesion, or from one who had had a lesion in the previous six months and was now a carrier.

ROLE OF THE PATIENT

Patients' noses acquire the hospital staphylococcus at the rate of about 10% per week, the increase being due partly to the colonisation of non-carriers and partly to replacement of an existing, usually harmless, staphylococcus. R. E. O. Williams et al. (1959), Weinstein (1959), and Colbeck et al. (1959) have shown that surgical patients who are carriers before operations are much more likely to become infected in the postoperative period than those who are non-carriers before operation.

Besides being a possible danger to themselves, by providing additional "breeding grounds" they contribute (perhaps very greatly) to the general staphylococcus load in the ward. Also, on discharge from hospital, they take home antibiotic-resistant staphylococci which cause infection later on or outbreaks of serious infection among their relatives and friends (Ravenholt et al. 1957, Wentworth et al. 1958).

The newborn baby's responsibility for its mother's breast abscess is well enough appreciated.

Visitors are of comparatively minor importance. Few of them carry dangerous staphylococci, and in this country even these are seldom resistant to anything other than penicillin. Thus if they do cause infections these are usually easily treatable. Nevertheless, ward sisters should have standing instructions to keep out visitors with boils, styes, and so on, except in very special circumstances.

METHODS OF CONTROL

Eradication.—To eradicate the staphylococcus from the nose of an established carrier is difficult. In about 70% of cases it can be removed by applying antibacterial creams just inside the nostril five or six times daily for at least a week (Gould 1955, Gould and Cruickshank 1957); but unfortunately, recolonisation occurs within a matter of weeks—either with a different strain or with the same strain (in this case probably from the person's clothes or from somewhere on the skin).

Eradication of nasal carriage should therefore be undertaken only when there is a definite indication, and it should always be accompanied by other measures to prevent recolonisation with the same strain.

Protection: Suppression.—To prevent a non-carrier from becoming a carrier, or to prevent a carrier from picking up a new strain, is relatively easy. In over 90% of cases a twice-daily application of antibiotic creams to the nostrils is adequate. Such treatment may be desirable to cover a period of special risk. It will rarely eradicate an already established staphylococcus, but during the period of its application, it will greatly suppress the growth of the organism, and prevent dissemination—which is the important thing.

PRACTICAL CONSIDERATIONS

Staff.—Because of the rapidity of recolonisation after treatment of carriers, eradicative treatment is justified only if the indications are definite. It is imperative for staff who are prone to staphylococcal lesions, or are found to be carrying a strain which is definitely known to be causing, or is likely to cause, infection. Treatment should be intensive for ten days (5 times daily), and protective for a month or two (twice-daily application). The person should also use nothing but antiseptic soap for toilet purposes, an antiseptic in the bath water, or antiseptic dusting-powder afterwards. (The harmlessness of this procedure and the frequency of perineal carriage in people with staphylococcal lesions justifies this as a routine, even without bacteriological diagnosis.) During this " protective " phase of treatment, all outer clothing should be sent to the cleaners, since staphylococci will survive for weeks in clothing and will cause reinfection or recolonisation of the skin. Though complete sterilisation of clothing is rarely practicable, dry cleaning will greatly reduce the number of staphylococci. After all this has been done, the staff member might be sent on a holiday in the hope that he or she will become recolonised with a harmless " civilian " strain of staphylococci. If there are repeated " relapses " the possibility of a close relative also being a carrier of the original strain and requiring treatment must be borne in mind.

Protective or suppressive treatment of the noses of staff on a mass scale is justified as part of an emergency campaign when cross-infection is rife, but it should be for two or three weeks only, while things are being brought under control. The work of Gould and Allan (1954) and Rountree et al. (1956) has shown how effective it can be on occasion; but as a long-term policy it is probably unjustified, for it can lead to unrest among the staff and probably to antibiotic sensitivity reactions. Staff should as a rule, be treated selectively, on the results of nasal swabbing.

TREATMENT OF PATIENTS

The objective here is to protect the patient against himself and against others, and others against him. Twice-daily application is adequate. Gillespie et al. (1959) produced evidence that the routine protection of patients in this way, together with certain other measures, will reduce the infection-rate of wounds. Such treatment may not always be effective in reducing the incidence of infection. Results by Henderson and Williams (1961) have been equivocal, and J. R. B. Williams et al. (1959) failed to control an epidemic by this means. The situation remains unclear. Meanwhile widespread trial of this method is justified by the theoretical case in its favour, by the simplicity and harmlessness of treatment, and by its cheapness compared with the cost of running a hospital bed. Old people who come into hospital with bronchitis or heart-failure often develop staphylococcal pneumonia. It would be interesting to know whether the onset of pneumonia is preceded by nasal carriage, and if so whether pneumonia complications of this sort might be prevented by prophylactic nasal treatment of all aged patients.

It is worth stressing certain essentials to a campaign directed at patients:

a. All nurses (not just ward sisters) must have the objectives and importance of the campaign explained to them in detail. Otherwise, treatment will not be carried out properly.

b. Each patient must be issued with a tube of cream and shown exactly how to apply it (this is important) as from the first day of admission. The patient is also given a simple explanation of what it is all about.

c. Other routine precautions against infection must continue to operate—i.e., aseptic and antiseptic techniques.

NEWBORN INFANTS

Simpson et al. (1960) have found that the frequent use of a hexachlorophane dusting-powder will reduce the number of infections in newborn infants, and breast abscesses in their mothers, to very low levels—so low that the use of nasal creams could barely improve things. On the other hand Spink (1960) in a controlled trial of nasal antiseptic creaming (once daily) in 1250 infants, found that the infection-rate in the babes was one-fifth, and in the mothers, one-half of that of the 1250 controls. Stokes (1960) in a smaller controlled study, and Jennison and Komrower (1961), have also obtained good results. Moreover, the medical literature contains several references to the successful control of outbreaks of infection by instituting nasal prophylaxis or treatment of infants (e.g., Duthie 1957, Klein and Rogers 1959).

In my opinion both powdering and nasal protection should be carried out. With powdering alone, the nasal carriage-rate on discharge is still high (30% or more), and if we do nothing about this we are sending home 30% of babies carrying a hospital strain of staphylococcus which must be a possible danger to themselves or to their contacts at home. Isbister (1959) found that the organism recovered from 17 out of 22 staphylococcal pneumonias in young children could be traced back to birth or stay in a hospital, or to a contact recently in hospital. The havoc caused by ex-patient carriers among their relatives at home has already been mentioned.

THE PRACTITIONER'S RESPONSIBILITY

The association between recurrent staphylococcal skin conditions (e.g., boils and styes), and nasal and perineal carriage, and the good results obtainable by treating the nasal and skin carriage (Gould and Cruickshank 1957, Tulloch et al. 1960), makes this treatment an essential part of therapy for the lesion itself. The procedure recommended is exactly as for " eradication " in the section on Hospital Staff above.

It is doubtful whether it is worth confirming the carriage state by bacteriological investigation, since the cost in man-hours lost by the patients and laboratory technicians far outweighs the cost of a tube of suitable antibacterial cream, and the risks of treatment appear to be negligible.

The relation between recurrent or relapsing staphylococcal otitis or sinusitis and nasal carriage has, so far as I know, not yet been studied; but probably a relation exists.

On encountering a case of staphylococcal disease of any sort, the general practitioner should ask the patient whether any member of his household has lately been in hospital. If so, the contact should be swabbed for bacteriological diagnosis of nasal carriage. If the report is positive, nasal treatment of the contact will be necessary. It may be surprising how often a newborn babe will prove to be the culprit.

OBJECTIONS TO TREATMENT OF CARRIERS

The case for treating the noses of patients and staff with staphylococcal lesions is now so well proved that we are hardly justified in withholding treatment. The case for protective treatment of patients, however, merits discussion. Objections have been raised on the following grounds:

1. That it will encourage the development of resistant strains of organisms.
2. That in clearing staphylococci from the nose we run the risk of colonisation by a more dangerous strain.
3. That sensitivity reactions to the medicaments used may occur.
4. That the treatment is troublesome to carry out, and distasteful.
5. That it is an unjustified additional expense.

Antibiotic resistance and sensitivity reactions are, of course, possibilities, but suitable choice of antibacterial agents reduces them to a minimum. Neomycin resistance has been reported from one hospital in the United States (Quie et al. 1960), and, since most preparations used for controlling nasal carriers contain neomycin, one might have expected neomycin resistance to have been reported. But Gillespie (1961) and Shooter (1961) have not yet encountered it. Lowbury (1960) has used neomycin, for several years, in combination with other agents, for the prophylactic treatment of burns, and has seen resistance only once. The combination of neomycin with another agent such as chlorhexidine may prevent neomycin resistance from emerging. But, even should resistance occur and infection develop, this would be no great tragedy since the drug is rarely used for systemic therapy. All that would be necessary would be a temporary change, for nasal prophylaxis, to some other preparation not containing neomycin.

In patients with a normal healthy skin sensitivity reactions seem to be rare.

The replacement of a harmless strain by a virulent one is very unlikely to occur while treatment is being maintained, and the risk seems well worth taking when we remember that, as things stand at present, patients in hospital acquire the more dangerous hospital strain at the rate of about 10% per week.

That the treatment is troublesome and distasteful is no doubt an objection; but, as Gillespie (1960) has said, it is hardly more trouble than cleaning the teeth. The provision of a small tube of cream for each patient makes it more acceptable. Careful explanation to the nurses, patience, and constant supervision are necessary to ensure full cooperation. At a conservative estimate 10,000–20,000 patients die from staphylococcal disease each year in the United Kingdom, and this justifies the effort.

COST

The prevention of one week's hospital stay by one patient in each ward every six months will save the cost of routine treatment of all patients with a cream based on neomycin and chlorhexidine.

OTHER METHODS OF TREATMENT

Nasal sprays.—Stratford et al. (1960) obtained good results with sprays containing antibiotic agents. Used once daily, the sprays seem to have given a higher clearance-rate than creams, and they may perhaps prove valuable for eradicative treatment of the established carrier. For prophylaxis over a long period, however, daily application of a little cream to the nostrils may be easier, less harmful, and more economical. Compared to creams, ointments are less effective and less acceptable.

SUMMARY AND CONCLUSIONS

Staff or patients with staphylococcal lesions are usually nasal carriers. If they are, they should have eradicative treatment of the nose, followed by protective treatment. This applies to domiciliary as well as to hospital practice, and the general practitioner has a real responsibility.

Hospital staff should be under fairly constant supervision, and carriers of known dangerous strains should be treated. The special dangers of convalescent staphylococcal carriers should be appreciated. A simple method for detecting the " carrier disperser " is required.

There is a case for protecting patients against acquiring the hospital staphylococcus in their noses, and a very strong case for protecting newborn babies.

People with staphylococcal lesions should be presumed to be carrying staphylococci on the perineal skin as well as in the nose. Antiseptic baths, the use of antiseptic soap, and antiseptic dusting-powders are necessary as well as nasal therapy.

I am very grateful to a large number of medical colleagues in hospitals for carrying out clinical trials of various antibacterial substances, for allowing me to quote unpublished results, and for giving up many hours of their time to discussions. In particular I would like to mention Dr. W. A. Gillespie, Dr. J. C. Gould, Dr. G. M. Komrower, Dr. R. F. Jennison, Prof. L. P. Garrod, Dr. R. A. Shooter, Dr. M. S. Spink, Dr. E. Joan Stokes, Dr. E. J. L. Lowbury, and Dr. R. J. Henderson. I must add, however, that the opinions expressed in this paper are not necessarily shared by them.

REFERENCES

Colbeck, J. C., Robertson, H. R., Sutherland, W. H., Hartley (1959) *Med. Serv. J. Canada*, **15**, 326.
Duguid, J. P., Wallace, A. T. (1948) *Lancet*, ii, 845.
Duthie, E. S. (1957) Report on a Symposium on Hospital Coccal Infections, arranged by Assocn. Clinical Pathologists, and M.R.C. Committee on Cross-Infection in Hospital.
Gillespie, W. A., Alder, V. G., Ayliffe, G. A. J., Bradbeer, J. W., Wypkema, W. (1959) *Lancet*, ii, 781.
— (1960) *Med. Press*, **243**, p. 536.
— (1961) Personal communication.
Gould, J. C. (1955) *J. Hyg., Camb.* **53**, 379.
— Allan, W. S. A. (1954) *Lancet*, ii, 988.
— Cruickshank, J. D. (1957) *ibid.* ii, 1157.
Hare, R., Thomas, C. G. A. (1956) *Brit. med. J.* ii, 840.
— Ridley, M. (1958) *ibid.* i, 69.
Henderson, R. J., Williams, R. E. O. (1961) *Brit. med. J.* ii. 330.
Hobbs, B. C., Carruthers, H. L., Gough, J. (1947) *Lancet*, ii, 572.
Isbister, C. (1959) *Med. J. Aust.* ii, 629.
Jennison, R. F., Komrower, G. M. (1961) *Brit. med. J.* i, 89.
Kinmonth, J. B., Hare, R., Tracy, G. D., Thomas, C. G. A., Marsh, J. D., Jantet, G. H. (1958) *Brit. med. J.* ii, 407.
Klein, J. O., Rogers, E. F. H. (1959) *New Engl. Med. J.* **260**, 1012.
Knights, H. T. (1961) Personal communication.
Lowbury, E. J. (1960) Personal communication.
Quie, P. G., Collin, M., Cardle, J. B. (1960) *Lancet*, ii, 124.
Ravenholt, R. T., Wright, P., Mulhern, M. (1957) *New Engl. J. Med.* **257**, 789.
Ridley, M. (1959) *Brit. med. J.* i, 270.
Roodyn, L. (1954) *ibid.* ii, 1322.

References continued overleaf

A SCHEME FOR RAPID TABLET IDENTIFICATION

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ATTENTION has been repeatedly drawn to the need for some means whereby tablets and capsules can be rapidly identified.[1] The extent of this need is suggested by the fact that in Britain more people die from poisoning than are killed on the highways.[2] We work in a hospital where more than five hundred cases of poisoning are dealt with annually. In cases in which poisoning has resulted from ingestion of a medicament, this has been in tablet form in some 60–65% of cases.

In hospital the pharmacist is often asked to identify a drug from a single tablet of it. For the speedy identification that is essential, he may derive some help from colour charts that have been published and from details given by manufacturers in their literature; but such information is somewhat fragmentary.

The scheme devised by us at this hospital is simple, speedy, and effective if a single whole tablet is available. It is based on the physical characteristics of tablets, such as size, colour, shape, markings, and coating; and the tablet is identified, or the possibilities narrowed, by comparison of its physical characteristics with those of known products.

Known tablets are dealt with as follows:

(1) The diameter of the tablet is measured by means of a micrometer screw-gauge and referred to the appropriate *B.P.* 1958 tablet size, given in thirty-seconds of an inch.

(2) Other characteristics then noted are:

(*a*) Colour—classification is limited to eight "basic" colours (red, brown, blue, green, yellow, purple, white, or multi) since a comparator rack containing the originals soon differentiates between, for example, pink and carmine although both are classified as red.

(*b*) Uncoated or coated, and type of coating (e.g., enteric).

(*c*) Marking and/or scoring (this is reproduced on the corresponding card).

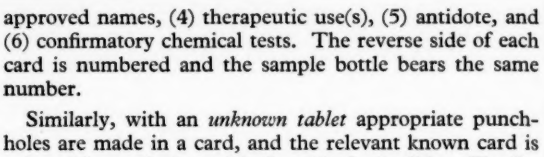
(*d*) Whether bevelling is present or not.

(*e*) Shape other than circular (e.g., triangular, hexagonal heart-shaped).

The appropriate punches are made on a card (see figure) by means of a ticket collector's punch.

Other items recorded on this card are: (1) name of tablet and strength, (2) maker's name, (3) proprietary and approved names, (4) therapeutic use(s), (5) antidote, and (6) confirmatory chemical tests. The reverse side of each card is numbered and the sample bottle bears the same number.

Similarly, with an *unknown tablet* appropriate punch-holes are made in a card, and the relevant known card is selected by exclusion with the aid of a bodkin. Finally,



The card.

the known tablet concerned (the number of which is shown on the back of the "known" card) is compared visually with the unknown tablet.

Each of more than a hundred requests for tablet identification have been successfully dealt with. These have come from the casualty department, dermatologists, neurologists, other consultants, and a public analyst.

The scheme may be suitable for adoption by forensic science laboratories and large general hospitals.

We are indebted to the many manufacturers who have willingly supplied samples of their products.

1. e.g. Wilson, G. M. *Lancet*, 1961, i, 1109. Whitney, J. D. W. *ibid.* p. 1229. Brown, H. M. *ibid.* p. 1284.
2. Cumming, G. Medical Management of Acute Poisoning. London, 1961.

DR. GREEN: REFERENCES—*continued*

Rountree, P. H., Heseltine, M., Rheuben, J., Shearman, R. P. (1956) *Med. J. Aust.* i, 528.
Shooter, R. A. (1961) Personal communication.
Simpson, K., Tozer, R. C., Gillespie, W. A. (1960) *Brit. med. J.* i, 315.
Spink, M. S. (1960) Personal communication.
Stokes, E. J. (1960) Personal communication.
Stratford, B., Rubbo, S. D., Christie, R., Dixon, S. (1960) *Lancet*, ii, 1225.
Tulloch, L. G. (1954) *Brit. med. J.* ii, 912.
— Alder, V. G., Gillespie, W. A. (1960) *ibid.* ii, 354.
Valentine, F. C. O., Hall-Smith, S. P. (1952) *Lancet*, ii, 351.
Weinstein, H. J. (1959) *New. Engl. J. Med.* **260**, 1303.
Wentworth, F. H., Muller, L., Wentworth, B. (1958) *Amer. J. publ. Hlth.*, **48**, 287.
Williams, R. E. O., Jevons, M. P., Shooter, R. A., Hunter, C. J. W., Girling, J. A., Griffiths, J. D., Taylor, G. W. (1959) *Brit. med. J.* ii, 658.
Williams, J. R. B., Talbot, E. C. S., Maughan, E. (1959) *ibid.* i, 1374.

MEDICAL PROTECTION SOCIETY

AT the annual meeting on Oct. 4, Sir CLEMENT PRICE THOMAS, the president, drew particular attention to some of the points made in the society's annual report. Sooner or later every practitioner meets the difficult or dissatisfied patient who makes a complaint; and, if that complaint comes before a medical service committee, however trivial it may be, the doctor should attend the hearing if he possibly can, or else write to the clerk explaining why he cannot. The need for accurate records is something on which the society's council feels strongly: "Impressions are notoriously inaccurate", said Sir Clement, "and the only true record is one that is written at the time." Having been himself faced with parents who, on religious grounds, have refused consent to blood-transfusion for their children, he felt that the society's legal advisers put the position clearly:

"The performance of an operation or the giving of a blood transfusion without express or implied consent constitutes an assault in law, but if a doctor obtains a written supporting opinion from a colleague that the patient's life is in danger if operation or transfusion is withheld and gets an acknowledgment (preferably in writing) from the parent or guardian that he refuses consent despite the explanation of the danger, the doctor, in our opinion, will run little risk in a Court of Law if he shows that he acted competently and in the best interests of the patient according to his own professional conscience."

Turning to types of case that come up frequently, Sir Clement said that nerve palsies might very often be avoided if it were realised that one of the safest places for an intramuscular injection is the large muscular mass on the outside of the thigh. Again, for intravascular injections "one cannot be too careful". He also mentioned a paragraph in the report referring to criticism of doctors for apparent failure to appreciate their statutory responsibilities in certifying the cause of death. "Really all that is required is that the 'best knowledge and belief' of the certifying practitioner should be tempered with a healthy and reasonable suspicion in cases of untimely death."

The report shows that last year the society's membership rose from 35,551 to 36,858, and the accumulated funds from £207,525 to £222,556. "The financial resources together with the very satisfactory re-insurance agreement with Lloyd's underwriters ensure that the indemnity granted to members is more than adequately secured without recourse to an increase in subscription which remains at £1 per annum for the first three years for the newly-qualified member and at only £2 per annum thereafter for both medical and dental members."

At the meeting Sir Clement Price Thomas was re-elected president, Mr. W. M. Mollison treasurer, and Dr. Alistair French secretary. Dr. H. A. Constable is deputy secretary, and Dr. J. Leahy Taylor has joined the staff as assistant secretary. The financial secretary is Mr. S. Rayner, and the solicitors Messrs. Le Brasseur & Oakley. The chairman and vice-chairman of council are Dr. F. Harwood Stevenson and Mr. H. L. Hardwick, and the society's offices are at 50, Hallam Street, London, W.1.

MEDICAL DEFENCE UNION

IN an address on Accident and Design in Surgery, at the union's annual meeting on Sept. 26, Prof. CECIL GRAY said that the number of cases dealt with since the introduction of the National Health Service was, in proportion to the increase in membership, really not significantly greater than in previous years. Hospital authorities could not see why they should indemnify a doctor against a claim for which he himself was mainly responsible; and a fortunate outcome of this reluctance was that the doctor remained independent of the huge organisation which employed him.

The Union, which covered 70 % of the doctors in the United Kingdom, where it had just over 45,000 members, had in 1960 dealt with 2837 cases: which meant that 1 in about every 16 got into some sort of difficulty in the course of each year. Some 14–15% of all complaints had to be referred to the solicitor; and of cases reported to the solicitor in which the primary issue was one of negligence, some 10–12% came to trial.

Speaking of specific hazards, Professor Gray suggested that it was wrong to vary the colour or shape of ampoules: nothing should encourage those using them to cut short the simple precaution of reading the label on the ampoule —not on the box, for this could be very deceiving. He sometimes wondered whether in hospitals all ampoules should not be put into one big box so that everyone had no alternative but to read the label on the ampoule.

He had found in his area no agreement on the nomenclature of digits. In his view those on the hand should be termed the thumb and the index, middle, ring, and little fingers, and those on the foot be designated by numbers. Likewise operating on the wrong patient might be avoided if each were labelled with his Christian name and surname, ward, hospital number, operation, and side. Professor Gray believed that the anæsthetist should be responsible for routinely checking that the right patient was submitted to the right operation.

Much could be done by local initiative to avert mishaps. Many hospitals held periodic morbidity conferences. If these were to succeed, certain conditions must be fulfilled: all, consultants and juniors, must play a part; the conferences must be carried out in a light and frank atmosphere; and they must be infrequent enough not to be too demanding on the participants' time and for there to be a general demand that one should be held. Professor Gray suggested for meditation Carlyle's dictum that "The greatest of faults . . . is to be conscious of none."

In its annual report the council refers to the large number of practitioners who discover—often belatedly—that their names have been erased from the Medical or Dentists Register as a result of the practitioner not receiving or replying to communications from the Registrar asking for his current address and whether he has ceased to practise. If the Registrar does not receive a reply within six months, the practitioner's name is erased. In consequence, the practitioner may unwittingly be practising illegally; moreover so long as his name is not on the Register he cannot claim the benefits provided by the Union.

The Union has sought fresh advice on the legality of sterilisation; and in the light of opinions expressed by English and Scottish counsel it seems that the propriety or otherwise of performing a sterilising operation can be summarised as follows:

1. Sterilisation on therapeutic grounds would be upheld by the court.

2. Sterilisation on well-founded eugenic grounds would also be upheld.

3. Sterilisation carried out merely on the ground of personal convenience (e.g., of a husband or a wife solely as a convenient method of birth control) might not be upheld by the court.

4. Where there was a clear element of moral turpitude and damage to the public interest (e.g., sterilisation of a prostitute for her convenience) the operation would, in all probability, be condemned by the court.

Occasional Book

THE CATARRHAL CHILD

THERE have been few planned studies to gather information about the child with recurring colds and coughs and other respiratory infections. Even the most basic information is lacking about this common situation. Very little is known about the natural history and epidemiology of upper respiratory disease in children, and even less about the true value of the many different treatments which are applied. A new book [1] on the catarrhal child is therefore especially welcome.

Dr. John Fry, as a general practitioner of Beckenham, Kent, finds that in his practice respiratory catarrh is responsible for nearly half of all the attention given to children under 10 years. In an average year 57% of all children under 10 were seen because they had coughs,

1. The Catarrhal Child. By JOHN FRY, M.D., F.R.C.S. London: Butterworths. 1961. Pp. 139. 25s.

colds, or catarrh. Fry points out not only that there are big differences among general practitioners in the way they deal with these patients but also that the cost of treating this group of children each year must be about £10 million. Much of this sum goes towards the removal of 250,000 pairs of tonsils and adenoids.

Clinically, three types of illness may be recognised: the acute cold with profuse running nose and irritating cough; persistent nasal obstruction and discharge; and a dry barking cough which often lasts most of the winter. A relatively high incidence of these disorders in the first 3 years of life was followed by a plateau at 4–8, and a definite decline after the 8th year. The coughs and colds seemed to be slightly commoner in boys than in girls, and they began at a younger age in children who had older brothers and sisters than in those who were the eldest or only children. Fry emphasises that management must be based on recognition that a phase of frequent coughs and colds is virtually normal in most children, who outgrow this phase after their 8th year. More severe respiratory disorders are less common.

Fry estimates that 1 child in 20 will have an acute chest infection in the first 10 years of life, and of these 10% will have more than one attack; but during the period of the study only 4% of these infections required admission to hospital. Some children went through a phase in the second 5 years of life when they were particularly liable to acute chest infection. In Fry's practice about 20% of all children had in their first decade one or more attacks of wheezing, which seemed to be a non-specific reaction to many stimuli. In children wheezing most commonly followed an upper respiratory infection: Goodall [2] noted that there had been such a preceding infection in 55%; and in Fry's series wheezing had been preceded by infection in 90% of 214 episodes. Mechanical factors may sometimes be responsible, including mediastinal-gland enlargement or inhaled foreign bodies. Mac Keith [3] suggested that sometimes wheezing may be related to emotional stress. Apparently attacks were commonest in the first 2 years of life and on starting school. There was no evidence that these wheezy children grew up to be chronic asthmatics.

Catarrhal children are prone also to acute otitis media. Over the ten years 778 attacks were observed in 333 children (99 attacks per 1000 children at risk). 67% of children who had had an attack had recurrences but complications were rare. Mastoiditis was diagnosed only twice; and myringotomy was never performed. The majority of children (64%) presented with earache and a red but intact drum. Of the remainder, the drum perforated with discharge in 26%. About 21% of those with an intact drum and 36% of those with discharge were judged to need antibiotics. There were no serious residual disabilities. Some deafness was noted in 1·2% a year after the last attack.

In only half the 475 episodes of acute throat infection could a specific cause be found by swabbing the throat. The condition was common in young children and in young adults but rare in infants (and in adults over 60). In children under 10 the age-incidence showed the usual peak between 4 and 8 but there was less seasonal variation, acute throat infections being common all through the year. The average untreated attack tended to settle spontaneously within three to five days. Only 2 cases of acute nephritis and none of rheumatic fever were seen in the practice during the ten years. Antibiotics were considered necessary in only 15% of acute throat infections. The tonsillectomy-rate was only 5% in children with these infections.

Removal of the tonsils is today the commonest surgical operation. One-third of all children admitted to hospital have their tonsils removed. It is estimated that in ten years 2 million children in Great Britain have had their tonsils removed at a cost of £30 million and with a loss of 350 lives. Is the very high rate of operation the result of an endemic disease or may it be due to some false beliefs? Variations, for instance, from district to district are quite remarkable and are explicable only on the grounds that doctors vary in their opinions.[3]

Who has the operation? Fry asks. The most popular age for tonsillectomy is between 4 and 8 years. In the past the operation was commoner in the upper social classes: now there is little difference. In Fry's practice, over ten years, 27 children have had one or other operation —a rate of 3% which is much lower than the rate of 20–30% in the country as a whole. The indications in these cases were either recurrent tonsillitis or recurrent otitis media. No permanent ill effects were associated with this low rate of operation. He suggests that before a decision is made to operate, the doctor should appreciate that these conditions have a peak at 4–8 years of age, followed by a natural decline, and moreover that they are now much less severe and less liable to complications.

Fry also believes that great care should be taken in deciding whether or not to use antibiotics in catarrhal children, since an unselective approach carries its dangers and also makes for a lazy attitude of mind in the physician and increases the drug bill unnecessarily. When Fry saw a case of acute respiratory infection he followed one of three courses: if the child was judged to be severely ill antibiotics were given at once; if he was less ill, it was considered safe and proper to observe the situation carefully for 24–48 hours, and at the end of this time he was either better and antibiotics were not required or he was not better, in which case antibiotics were used. With this approach it was found, over three years, that antibiotics were given in 53% of all acute chest infections, in 12% of all acute throat infections, and in 23% of all cases of acute otitis media.

Last, but not least, as Yudkin [4] has illustrated, is the importance of the attitude of the mother and the effect that the child's condition has on her. Young parents seeking perfection in their firstborn are always likely to worry. The mother may blame herself for her child's recurring illnesses and feels that she is failing in her standards as a mother. A major part of management is reassuring her, restoring her confidence, and convincing her that it is really a natural process which the child will outgrow and for which she is in no way to blame. Dr. Fry suggests that to meet these challenges of providing a good service to the children in his practice, the family doctor should organise his practice to *encourage* mothers to seek his advice on all problems of child care and development.

2. The Health of the School Child: Report of the Chief Medical Officer of the Ministry of Education, 1958 and 1959. H.M. Stationery Office, 1960.
3. See *Lancet*, 1961, i, 154.
4. Yudkin, S. *ibid*, Sept. 9, 1961, p. 561.

In England Now

A Running Commentary by Peripatetic Correspondents

"Elizabethan in its boldness of concept!" was how a British Railways spokesman described their plan for raising the sides of their slag-trucks so as to carry four more tons of slag. But was he certain that this was quite the adjective of choice, we asked, with visions of a furious Cappy (Art tha sleepin' there below?) Drake surfacing like a Polaris missile. "Well, really!", he replied, petulantly kicking a FRAGILE package, "when today the number of slag-truck wheels collapsing under the extra strain has reached a new low, and by as early as the end of November all main lines should be clear of wreckage!" Meanwhile, North-bound passengers are routed Fishguard to Cork, and thence by jaunting-car for ultimate repatriation at Stranraer.

Following this pronouncement, as if the Affluent Society had not had enough excitement for one week, the Ministry of Incoordination took the liberty of interrupting the '*Strikers' Playtime* radio programme to announce the erection of gigantic steel samovars on the highest points of all our National Parks. From these, tea will be piped into every workshop and factory in this scepter'd isle and a shop-steward will only have to open his yap to have it filled with hot tea. The first pipe-line goes to the Dagenham area and will be uncorked by Sir (as he will then be) Sidney Spout, the tannin-toughened, terrible-tempered president of the 157-million strong Union of Char-sloppers and Stirrers. Mr. (as he now is) Sid Spout, "Mr. Cuppa" himself, said at Blackpool today that this was yet another attempt to dilute the workers' tea. Tea contains energising, health-giving tannic acid and should be free on the National Health, while tannic-acid deficiency should be included for compensation under the Act. Furthermore, this pipe-line scheme tried to sabotage his union's demand for a non-stop tea-break from Monday morning to Saturday afternoon, and if the bosses thought that this meant the lads would stand for having their dinner-hour included in their tea-break, they'd as much chance of getting away with it as an octogenarian bank-clerk carrying the cash through Soho in a string-bag. Too long had the workers winced under the lash of tannic acid deprivation and it was now up to the Government as to which came out first—his lads or the Honours List.

* * *

Out of the heat of sun-drenched Rome, the cool auditorium of the palazzo was a place to relax after lunch while the array of distinguished persons on the distant stage went through the movements of Opening a Congress. Earphones on, we switched the selector knob to hear which of the translators was winning the race with the speaker and watched the photographers wandering to-and-fro, up and down the aisles, across the platform, behind, between, round and in front of the speakers. Public speaking is thirsty work; how thoughtful then was one of the camera-men. He had arranged to have a crate of mineral water brought to the platform. A bottle was discreetly put at the elbow of each of the distinguished presidents, secretaries, leaders of delegations, and glasses filled for them. More photographs, but just before each picture the bottle was quietly placed forwards to the front of the table, label square to the camera. Watching the skill with which it was shown in black-and-white that distinguished medical men prefer a certain water relieved the tedium of a rather dull ceremony. The only drawback was that having no field-glasses to read the label I still do not know which bottled water to drink to give me at least renal distinction, if no more.

* * *

Of all the mysteries of medicine to the lay person, one of the greatest is the value of the throat-swab. Our child gets a temperature and inflamed tonsils, and my husband, a conscientious pædiatrician, orders an antibiotic and takes a throat-swab. The throat-swab is sent to the laboratory and I arm myself with a bottle and teaspoon and prepare for a week of disturbed nights. After five days my husband says the antibiotic was not the best one according to the report and we are to change to 8-hourly administration of another type. After a few days he takes another throat-swab. Why, I ask—so that we may know in a week's time how he was today? I get a pitying smile.

* * *

One of the charming relics of Victorianism in medicine is the Commandment: Nurses shall not speak with hospital porters. It's particularly heavily enforced in those bastions of the Establishment, the London teaching hospitals. Where I trained, however, things are made entertainingly awkward for the Regimental Police by the fact that porters and students wear the same short white jackets. Slightly embarrassing mistakes have occurred. My friend James tells me he was walking along the corridor in white jacket on the way to a teaching round, and was given a neighbourly good morning by a probationer nurse of his acquaintance. Suddenly, he said, everything began to happen at once. A stentorian drum-shattering shout (Caterham Force Five) of "NURSE" rang out, and the whole joint appeared to explode in a flash of light. Out of the corner of his eye James noted the green-clad Junoesque figure of the Matron, to whom he is more allergic than the seed of grass in summer, and fled on the wings of the blast, but not before hearing: "Nurse, how DARE you speak to that porter?"

James, a sensitive soul, was rather hurt at not being immediately taken for the consultoid material he imagined himself to consist of, but he got over it in time. He was glad to qualify, however, and to exchange his short white coat for a longer one. What happened then was, I suppose, inevitable. Admitting a patient on an unknown ward, dressed in his new long white coat, he was carrying the rectal tray to the bedside when the Sister caught sight of him. "You're late, barber" she remarked grimly. "Pubic shave number 6, please." And swept off.

I think it's just that he looks older than the rest of us.

* * *

My wife now sends me to do the washing in the launderette round the corner, and I find my mind soon begins to wander as I sit and watch the sheets and towels and nappies spinning themselves dry in a machine which only needs a penny to set it in motion. "Spending a penny" this way has more lasting results than in other situations. It might have wider implications. Why not put baby in it once a day instead of all those dozens of nappies? What about the puppy—he's not house-trained yet. Little would he suspect it if I picked up the car keys and said "Let's go for a spin."

The plump woman with a wet load of washing nudged me. "Could you take your things out of the dryer? It stopped spinning long ago."

* * *

The other day I had to give a long intravenous injection to a colleague. He had had a lot of colic for three days, and was weak and dehydrated having continued with his work during two of those days. He fainted in the midst of my injection, and I prayed that it was not a drug reaction. As he came round after a few seconds, I realised that I was not feeling so good myself, with still another 10 c.cm. (ml., if you prefer it) to go. I was coming out in a profuse cold sweat, feeling wobbly about the knees, and was aware that my surroundings seemed to be more detached from me than they should. Summoning as firm a voice as I could manage, I called for a stool on which to sit, and managed to hold on. As I finished I reflected that I really would have looked a Charlie, out "cold" on the floor, with the patient equally cold and pulseless on the table, with blood dripping from the needle still in his vein.

* * *

All this rhyming paresis and thesis
With dysdiadochokinesis
Stems not from the praxis
Of iatro-didaxis
But simply from peripatesis.

Letters to the Editor

MEDICAL STAFFING OF CASUALTY DEPARTMENTS

SIR,—No indication can be seen at present that this question will ever get any easier. Recognition that this work is very difficult, responsible, and essential has been long in coming. Some regional hospital boards are now appointing senior casualty officers, but these doctors cannot cover the work 24 hours a day, 7 days a week, and they need holidays and sometimes they may be ill.

Many hospital residents now are overseas graduates. When the Commonwealth countries arrange their own postgraduate training the supplies of these doctors will dry up. The first departments to suffer will be the casualty rooms, because to young doctors the work there is as frightening as anæsthetics and less rewarding because it does not lead to postgraduate diplomas.

I should like to put forward a possible partial solution. The National Health Service regulations lay it down that every member of the medical staff must retire from hospital work at the age of 65. Undoubtedly we shall all look forward to being relieved of some of our work by the time we get near to retiring age. On the other hand, many doctors at 65, if they are fit, would like to continue with some part-time medical work at a less exacting level, if only such an opening were created. Many hate the idea of having to cease working when they still have years of useful and satisfying work in them. To the retiring consultant casualty work may be as easy as it is strange to the inexperienced young doctor. I therefore suggest the Ministry of Health should create a new type of senior part-time casualty post to which doctors can be appointed at the age of 65. The posts could be renewable on a yearly basis. If superannuation rights could be guarded it may even be found that some doctors may wish to change to such a post even before they are 65.

A casualty department could even be staffed entirely by four or five of these doctors who would carry out the duties in rotation. On the other hand, even a single doctor of this description, working five or six mornings only each week, would be of very considerable help.

If I, myself, were mentally and physically fit at the age of 65 I would much prefer work of this kind to enforced idleness.

Royal Albert Edward Infirmary, Wigan. F. R. ZADIK.

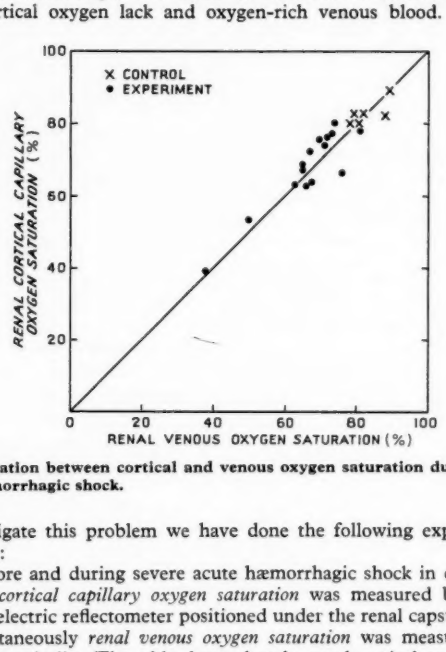
RENAL CIRCULATION DURING ACUTE HÆMORRHAGIC SHOCK

SIR,—In their interesting communication Dr. Jirka et al. (Sept. 23) argue in favour of arteriovenous shunting ("Oxford shunt") in the kidney during acute hæmorrhagic hypotension. The experimental basis was the finding of a decrease in renal vascular resistance and in *p*-aminohippuric acid extraction together with a cineradiographic demonstration of 10% reduction of the perfused area in the kidney. Their conclusion finds support in the recent anatomical studies of Gömöri.[1] The interest from the Oxford-shunt viewpoint lies in the discussion on renal hypoxia as the possible cause of acute renal failure.

It has repeatedly been demonstrated in dogs that in acute hæmorrhagic shock the renal venous oxygen saturation remains rather high (about 60%), the lowest values reported being 40–50%.[2–4] Although a venous oxygen saturation of 40–50% or more is not indicative of oxygen lack in the kidney, renal cortical hypoxia cannot be excluded despite a high venous oxygen saturation, since a shunt would allow the combination of cortical oxygen lack and oxygen-rich venous blood. To investigate this problem we have done the following experiments:

RENAL CORTICAL CAPILLARY OXYGEN SATURATION AND RENAL VENOUS OXYGEN SATURATION DURING HÆMORRHAGIC SHOCK

Dog	Mean arterial blood-pressure (mm. Hg)	Renal venous oxygen saturation (%)	Renal cortical capillary oxygen saturation (%)	Venous and cortical oxygen difference (%)
A	Control 118	80	82	− 2
	Exp. 48	73	77	− 4
	Exp. 34	50	53	− 3
B	Control 125	89	89	0
	Exp. 60	74	80	− 6
	Exp. 57	63	63	0
	Exp. 46	76	66	+10
C	Control 129	88	82	+ 6
	Exp. 41	72	76	− 4
	Exp. 32	66	63	+ 3
D	Control 130	80	80	0
	Exp. 50	70	75	− 5
	Exp. 60	71	74	− 3
E	Control 140	79	80	− 1
	Exp. 50	67	64	+ 3
	Exp. 40	38	39	− 1
	Exp. 60	65	67	− 2
	Exp. 60	65	68	− 3
F	Control 115	82	82	0
	Exp. 60	81	78	+ 3
	Exp. 50	67	72	− 5



Correlation between cortical and venous oxygen saturation during hæmorrhagic shock.

Before and during severe acute hæmorrhagic shock in dogs *renal cortical capillary oxygen saturation* was measured by a photoelectric reflectometer positioned under the renal capsule.[5] Simultaneously *renal venous oxygen saturation* was measured manometrically. The table shows that the renal cortical oxygen saturation was on average 68% during shock, the highest value being 80% and the lowest 39%. The figure demonstrates that there was a close correlation between cortical and venous oxygen saturation during hæmorrhagic shock as well as in the control periods. *This shows that there is no significant shunting with respect to oxygen during hæmorrhagic shock.*

The data of Jirka et al. in combination with ours suggest that damaging renal cortical hypoxia does in all probability not occur in acute hæmorrhagic shock despite the cortical ischæmia. That hypoxia does not occur is probably due to the fact that the essential work of the

1. Gömöri, P. *Excerpta Med.* 1960, Congress series, no. 29, 42.
2. Dole, V. P., Emerson, K., Jr., Phillips, R. G. A., Hamilton, P., Van Slyke, D.D. *Amer. J. Physiol.* 1946, **145**, 337.
3. Kramer, K., Deetjen, P. *Excerpta med.* 1960, Congress series no. 29, 50.
4. Lassen, N. A., Munck, O., Thaysen, J. H. *Acta physiol. scand.* 1961, **51**, 371.
5. Kramer, K., Graf, K., Overbedk, W., Zaun, H. *Pflüg. Arch. ges. Physiol.* 1956, **262**, 285.

kidney—sodium transport—is abolished during severe hypotension, so that the demand for oxygen is reduced.

The above data will be published in detail in *Pflügers Archiv ges. Physiologie*.

Bispebjerg Hospital, Copenhagen.
OLE MUNCK
NIELS A. LASSEN.

Institute of Physiology, University of Göttingen.
PETER DEETJEN
KURT KRAMER.

SIR,—The findings of Dr. Jirka and his colleagues are supremely important to the obstetrician, among others.

Bálint, in a lecture recently at University College, had already blazed the trail when he outlined four cardinal findings in hæmorrhagic hypotension. By direct measurement he had shown that in hæmorrhagic hypotension the *p*-aminohippuric-acid clearance (CPAH) was a considerable underestimate of the true renal blood-flow. Arguments based on the validity of such clearances, hitherto held to be impeccable, have been much used in attacks upon the shunting demonstrated by Trueta et al. Findings of such considerable import have underlined the validity of the Oxford views, and the Prague workers have confirmed this.

Bálint had also shown that the renal fraction of cardiac output did not change for 20 minutes (a fact confirmed in these recent findings and even that it actually *rose* thereafter). The oliguria, it may therefore be inferred, could not be related to a deficient renal blood-supply due to the hypotension after the hæmorrhage—an explanation offered by Oliver et al. and others. Here again there was conflict with CPAH findings which fell considerably. It was also shown by direct measurement by both Bálint and Jirka et al. that contrary to the CPAH findings, which indicated a rise in the total renal resistance, this resistance was directly related to the blood-pressure.

One other common finding was that some degree of selective vasoconstriction took place in the kidney in the later stages of hypotension. Jirka et al. confirmed this by cine-radiography, which indicated that during the hypotension the cortex of the kidney (in these cases, of the dog) remained unperfused. This change was recognisable *quite early* in the hypotension, and the high renal blood-flow is explained by the opening up of arteriovenous shunts—i.e., perfusion areas where the blood-flow is not affected by the nephron. It seems valid to include in these areas the juxtamedullary nephrons where afferent and efferent are similar in diameter, so that the glomerular filtration pressure (and hence urine formation) and the glomerular resistance in the renal circulation are presumably much reduced.

That these findings in oliguria are not peculiar to hæmorrhage and its hypotension is evident when the effects on renal function of bleeding due to placenta prævia are compared with those of *concealed* accidental hæmorrhage. Anuria seldom develops in placenta prævia, but is a considerable risk in concealed hæmorrhage, indicating a further ætiological process—the uterorenal reflex. Clinical proof of the existence of this reflex is found in the wonderful results of treatment by the Dublin school of obstetricians, who, in keeping with this hypothesis, rupture the membranes to overcome the uterorenal reflex and apply conduction anæsthesia reaching the level of the lesser splanchnic nerve, which supplies the kidney, to overcome the reflex cortical renal ischæmia, the basis of the anuria.

These visualised cortical renal changes in which diversion of blood-flow to the juxtamedullary area occurs, when correlated to the anatomical differences of the glomeruli of cortex and juxtamedullary areas, alone serve to explain the mechanism of so-called " afferent " and " efferent " glomerular vessel constriction—the need for which also prompted Pappenheimer's explanation of a hypothetical post glomerular circulation.

That evidence of such importance still remains largely parochial was clear at the 3rd World Congress of Gynæcology and Obstetrics in Vienna last month, when the paramount importance of glomerular ischæmia in anuria was again denied in favour of tubular necrosis.[1]

Since anuria in eclampsia is the climax of the toxæmic state, less severe stages of renal cortical ischæmia must underlie preclampsia. Of this much proof has been adduced in the past,[1 2] proof which is indirectly and largely endorsed by the very important researches of your contributors from Prague which have placed all of us heavily in their debt.

Worthing, Sussex.
JOHN SOPHIAN.

DOCTORS FOR THE FORCES

SIR,—Your very thoughtful leading article of Sept. 23 appears none too early. As one who during his early professional life in the Armed Forces and subsequently had the opportunity of discussing this subject with many young doctors, both married and single, may I make a few suggestions?

Bad publicity makes Service life unattractive. National Service officers returning to civil life have not enjoyed their experiences and are now bad publicity agents. Apparently no-one has explained to prospective young officers that they have ample time during their service to attend hospitals, laboratories, or lectures on many subjects, or to undertake research themselves, as is now being done by members of the College of General Practitioners. There is ample material available.

Loss of freedom to prescribe is mentioned. Surely as much freedom could be given as is enjoyed by general practitioners in the National Health Service, which is fair and reasonable.

If any business or other firm wants medical officers of any type or grade they are not only willing to pay the market price but also to see that suitable accommodation is provided, or an allowance in lieu: if they did not they would not get their men.

It is very important that the Services should not be considered as an inferior form of life, only suitable for second-class minds. There must be a strong financial attraction putting the holder in at least as good a position as he would have been if he had entered the National Health Service instead.

Insecurity, I suppose, is the most dreaded of all the objections that have been given to me. The haunting fear of all doctors going overseas or who take short-service commissions or appointments is " When I come home shall I be able to get suitable employment again?" Things, I am told, are much better managed in America, where Service doctors returning to civil life have priority over others in the search for employment.

Worthing. HAROLD LEESON.

CONTROL OF INFECTIOUS HEPATITIS

SIR,—The article of Oct. 7 by Dr. Milliken Smith states that " a study of the way the beds were arranged in the dormitories, and the seating in the dining room, indicates that infection was spread by personal contact, presumably by droplet infection ". Your readers will know that this route of infection is not the one now accepted for this disease.

In a series of 25 cases met in this practice ten years ago and spreading over a period of more than twelve months, the source of infection was found to be a mental hospital about 2 miles away from the village. This hospital employed certain women in the village as auxiliary nurses and kitchen hands. At the beginning it was noted that all cases were found in the cottages in the village rather than in the newer council houses. We therefore assumed that there was some relation between the crowded conditions in the cottages as distinct from the more hygienic conditions in the newer houses. Towards the end of

1. Hamburger, J., Crosnier, J., 3rd World Congress of Gynæcology and Obstetrics (in the press).
2. Sophian, J. Toxæmias of Pregnancy. London, 1953; *Excerpta Med.* 1958, **11**, no. 1.

the epidemic, however, 4 or 5 cases were noted in these new houses, and not until we took note of the kitchen arrangements were we led to suspect why this had happened. In every single case the families concerned had previously lived in one of the cottages and in each case they had transferred their methods of washing-up to the new house. This means that they used a kettleful of water in a bowl on the kitchen table rather than the more plentiful supply in the sink.

Unfortunately it proved impossible to keep a check on all these cases and a very interesting series was lost. There was sufficient evidence at the time, however, to justify a conclusion that the route of infection was by the gastrointestinal tract, and having regard to the number of cases arising in families where this method of washing-up was practised, whether in cottage or new council house, we were forced to the conclusion that this was a major cause of infection. May it not be that in the outbreak at Loddington Hall there was someone in the kitchen who was a carrier?

Great Glen,
Leicestershire. G. A. STANTON.

TREATMENT OF DISC LESIONS

SIR,—It is very difficult to diagnose intervertebral-disc protrusions with certainty unless they are verified by operation—and while agreeing with Dr. Stanton (Oct. 7) that the majority of patients will improve with conservative treatment, it is difficult to be sure which of these had an actual disc protrusion—by which one means a tear and protrusion of the annulus. If there is no tear, or a small one, the probability is that the patient will recover with purely conservative treatment, but if there is a large tear they will probably continue to have recurrences, at any rate, for some years, and, as the results of surgical removal of a torn annulus are so good, it is usually wise to advise operation in an otherwise fit patient.

Robert Jones & Agnes Hunt
Orthopædic Hospital,
Oswestry. ROBERT ROAF.

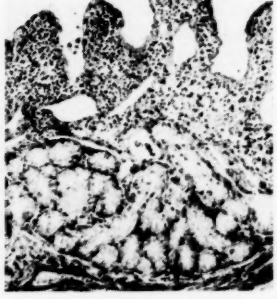
A MUCOLYTIC AGENT IN CHRONIC BRONCHITIS

SIR,—Dr. Palmer (Oct. 7) describes the interesting application of the mucolytic action of oxidised ascorbic acid to the problem of reducing the viscosity of sputum.

In this laboratory, oxidised vitamin C has been used over the past eighteen months to obtain suspensions of gastrointestinal mucosal cells for mixed cell agglutination experiments. This method of cell dispersal (to be published) employs one 'Ascoxal' tablet dissolved in 100 ml. of water. Pieces of fresh gastrointestinal mucosa, after standing in such a solution, readily shed their mucosal cells.

It would be imprudent to argue too exactly from the effect on gastrointestinal tissue in vitro to that on bronchial and alveolar tissue in vivo; other substances, such as trypsin, which are used for cell dispersal, have also been inhaled by many patients without untoward effect, as Dr. Palmer notes. Nevertheless, the manner in which a solution of oxidised ascorbic acid fifty times less concentrated than that used by Dr. Palmer, can strip gastrointestinal mucosa bare of its mucosal cells (see accompanying figures) should perhaps be borne in mind before the method is used more widely and possibly more energetically.

Normal duodenal mucosa (×75).



Duodenal mucosa exposed to ascoxal.

Department of Pathology,
Clatterbridge General Hospital,
Bebington, Wirral. W. K. COWAN.

"THE INDUSTRY IT DESERVES?": A DISCLAIMER

SIR,—Some of your readers have erroneously assumed that I wrote this anonymous article last week, since the title is attributed to me. I should like to make it clear that I had nothing to do with it.

Pinner, Middlesex. T. B. BINNS.

*** In our efforts to give Dr. Binns the credit for his arresting phrase, we have to our surprise and regret caused him embarrassment. We apologise to him and to those readers who were misled by our footnote. Dr. Binns had no knowledge whatever of the article before it appeared.—ED. L.

RECRUITMENT AND TRAINING OF MENTAL NURSES

SIR,—It is encouraging to receive suggestions from senior medical officers regarding the training and recruitment of psychiatric nurses, but the opinions expressed by Dr. O'Gorman (Sept. 23, p. 708) are somewhat misleading since many of the facts can be questioned.

The suggestions for a different system of training are based on the assumption that rewarding and interesting work which nurses could do has been taken from them by ancillary workers. The assumption can be shown to be false.

What is recognised by the whole of the profession as the most advanced type of training in the country has been in operation since 1957. The majority of progressive psychiatric hospitals, if not actually participating in this experiment, have applied to the General Nursing Council for permission to transfer. The 1957 syllabus is completely unrelated to general nursing and, although no assessment has yet been made as to its failings or successes, opinion is all in its favour.

We are surprised at the use of the term "mental deficiency" hospital—a now obsolete description.

The opinion that the course is too difficult may be based on the fact that the procedure for selecting students is inadequate. Provided the students are selected as recommended by the G.N.C., there should be no great difficulty in their mastering the subject, whether they are from this country or from overseas.

As to length of training, we disagree that it is too long. The nurse may learn the contents of the syllabus in a shorter time, but psychiatric nursing is an art and requires this period for confirmation of theoretical learning. Shorter periods are possible for nurses already on one part of the Register. Integrated schemes can also be arranged.

The problems in hospitals for the subnormal are no doubt somewhat different from those in the hospitals for the mentally ill, but surely the proportion of patients requiring feeding and cleaning is approximately the same—severely subnormal compared with severely demented? This care will always have to be given to the minority of patients, but to generalise is to give a false impression. Over 90% can be successfully trained, taught, and rehabilitated and their confidence restored if the nurses are given the opportunities. The main reasons for lack of these opportunities may be resistance of the medical staff to the fact that nurses are capable of psychotherapy and that planning for this type of nursing is lacking. The mental

nurse is a specialist just as much as the social worker and the occupational therapist, and failure to allow her to play her part is the fault of the hospital and not the G.N.C.

The different system Dr. O'Gorman suggests does not take account of the present training of occupational therapists and social workers, who do experience ward and field work in their training. In this hospital our colleagues, the occupational therapists, do not cease their activities at 5 P.M. They often work far into the evening and during the weekends, whenever they are required to do so.

To set up nurses in opposition to social workers and occupational therapists would be disastrous. Experience is vastly different from a qualification. The present-day psychiatric nurse is well trained—a specialist in psychotherapy. If this fact is not appreciated it is obvious that envious eyes will be turned towards the occupational therapists and the social workers.

Nurse Training School,
Bexley Hospital,
Bexley, Kent.

CATHERINE FORMAN
MICHAEL N. SAUNDERS
Tutorial Staff.

EXTERNAL CARDIAC MASSAGE

SIR,—In view of the widespread attention to external cardiac massage the following experience might be of interest.

Yesterday I was called urgently to the operating-theatre by a surgeon who had been carrying out urethral dilatation under local analgesia on a 66-year-old man. During this procedure the patient collapsed. When I saw him he was having a convulsion and was very cyanosed. Ventilation with pure oxygen was impossible owing to the spasms, so 0·25 g. thiopentone was administered. The spasms then disappeared and ventilation with oxygen through a face mask became easy, but by this time the patient was pallid and after a dozen or so large breaths with pure oxygen no improvement in colour was evident. The radial pulse was impalpable and it was concluded that the heart had either ceased to contract or was contracting so feebly as to be ineffectual. Intermittent pressure with both hands on the lower end of the sternum was started, as described by Kouwenhoven,[1] a fair amount of force being necessary to move the sternum adequately. Meanwhile, the face mask was held in position by a nurse. After about one minute the patient's colour gradually began to improve and several minutes later the pulse became palpable. At no time were the pupils seen to dilate, but spontaneous respirations did not return for ten minutes or more and became established only after a further lapse of time, indicating that there had been severe cerebral hypoxia.

This experience has led me to the conclusion that there is a reasonable chance of reversing cardiac arrest even when only one worker is present. Although expired-air respiration is the method of choice for simple artificial respiration, it is hardly feasible where closed chest cardiac massage is being carried out, for the movements of the sternum in this procedure cause a considerable movement of air in and out of the chest which would be adequate in an emergency and which, moreover, would probably conflict with the movement of air from simultaneously applied expired-air respiration. It is interesting to note that in one of the cases quoted in the American literature external cardiac massage was performed for some time by a policeman, and I feel that there might well be a case for teaching this technique to intelligent first-aid workers.

The decision when to perform expired-air respiration and when to perform external cardiac massage might not be easy; but expired-air respiration might be used for simple cyanosis, which is almost always accompanied by a bounding pulse, and external cardiac massage where pallor, pulselessness, or dilated pupils are present.

The patient has apparently recovered well, the only after-effects being pain in the lower ribs (the chest X-ray is normal), and complete amnesia for the time immediately before and after the operation. Indeed, the patient was most impressed at having no recollection of his trip to the theatre.

I am indebted to Mr. L. A. H. Snowball for permission to publish details of this case.

Willingdon,
Eastbourne,
Sussex.

P. H. VENN.

1. *J. Amer. med. Ass.* 1960, **173**, 1064.

SAFE AIR AND MOTOR-CARS?

SIR,—You mention (Oct. 14, p. 883) the concern felt by the National Society for Clean Air about the pollution of air by road vehicles. Since, as you point out, well-maintained vehicles may emit excessive smoke, and since it is at present very difficult to clean exhaust gases, it would surely be sensible to arrange for the exhaust to be discharged vertically upwards, as high up as possible. There can be little doubt that city streets would be cleaner and healthier if buses discharged their exhaust at roof level. It would presumably be much easier to enforce regulations about the level of discharge of exhaust gases than it is to enforce regulations about the adjustment and operation of engines.

Department of Physiology,
Queen's University of Belfast.

A. D. M. GREENFIELD.

RETROBULBAR NEURITIS IN PERNICIOUS ANÆMIA

SIR,—It is hard to give a definite answer to Dr. Hift (Sept. 23) without having precise details of his experimental methods. However, it does seem that he has misinterpreted my original hypothesis (May 6) and subsequent rejection of Dr. Matthews' argument (June 10) that cyanide may merely function by splitting cyanocobalamin from its binding protein. This argument depends on the assumption that the serum-B_{12} level consists solely of cyanocobalamin or that the available hydroxocobalamin is not converted to the cyano form by cyanide addition. As hydroxocobalamin is available, I find it exceedingly difficult to believe that it will not combine with cyanide under these conditions and would be pleased to hear Dr. Hift's explanation of this point.

The results of serum-B_{12} assay using *Lactobacillus leishmanii* have been subjected in the past to considerable confusion because some workers used cyanide extraction and others did not. This was pointed out by Dr. Matthews. It is only when cyanide extraction is used that the results are comparable to those using *Euglena gracilis* and this non-cyanide discrepancy surely cannot be accounted for solely by a splitting hypothesis.

When I referred to so-called normal subjects I was pointing out that in this context smokers could not be classified as normal and that this fact had not previously been taken into account. It has *always* been my contention that vitamin B_{12} in the form of cyanocobalamin and hydroxocobalamin is bound in different proportions of the one fraction to the other and that a major factor in this phenomenon was the exogenous and endogenous influence of cyanide on normal cyanide metabolism with its possible far-reaching effects on body enzymes.

When Dr. Hift refers to B_{12} I assume that he means cyanocobalamin. At the recent European symposium on vitamin B_{12} and intrinsic factor much fresh evidence was produced in support of the physiological status of hydroxocobalamin and it seems probable that the clinical era of this compound is about to begin.

As I have always believed that hydroxocobalamin is the potent physiological analogue of vitamin B_{12}, and made this quite clear in my original letter, I would be interested to see what interpretation Dr. Hift would place on his

experiments if these were repeated with radioactive hydroxocobalamin. In the interim I am grateful that he has shown an interest in the role of cyanide in body metabolism, since the elucidation of this problem may well have many important clinical implications.

Department of Medicine,
The General Infirmary,
Leeds.

A. D. M. SMITH.

SIDE-EFFECTS OF TRANYLCYPROMINE

SIR,—Tranylcypromine (' Parnate ') has recently been recorded [1] as causing spasmodic hypertension associated with severe headache.

A man aged 30 was admitted to University College Hospital with a one-hour history of severe headache, initially occipital, but subsequently spreading all over the head. He complained of feeling frightened and " unreal ". No other relevant history was obtained.

He was cold and sweaty. His pulse was regular (84 per min.) and blood-pressure 200/120 mm. Hg. There was slight photophobia but no neck stiffness. No other abnormal signs were found. Within two hours the blood-pressure had fallen to 140/80 and his headache disappeared gradually over the next two days. A lumbar puncture five days after admission revealed a slightly raised protein level (55 mg. per 100 ml.) with a very weak positive globulin, but was otherwise normal. Urine collected shortly after admission contained no excess of pressor amines.

It was later discovered that for three days before admission he had had tranylcypromine 10 mg. t.d.s.; his hypertensive episode so closely fitted the description by Dr. Clark [1] that it seemed reasonable to attribute the attack to the drug.

London, W.1.

M. ALDRIDGE.

University College Hospital,
London, W.C.1.

NIGEL OAKLEY.

GLUCOSE-6-PHOSPHATE-DEHYDROGENASE DEFICIENCY

SIR,—In some cases of neonatal jaundice without blood-group incompatibility, a deficiency of glucose-6-phosphate-dehydrogenase (G.-6-P.D.) has been found in the erythrocytes. Weatherall [2] has published details of 3 Malay families, in which severe neonatal jaundice with kernicterus was associated with this deficiency. Doxiadis and his coworkers in Greece,[3] after investigating the activity of G.-6-P.D. in erythrocytes from infants with icterus neonatorum of unknown ætiology, confirmed that most of their cases had this deficiency.

These two groups of workers used the colorimetric method of Motulsky and his colleagues.[4] In this procedure enzyme activity is assayed by estimating the time required to decolorise a dye—brilliant cresyl-blue. This has been used as a screening test. Its advantages are its rapidity and simplicity and only a small quantity of blood is needed. In our own studies of different problems in neonatal jaundice we have used Motulsky's method as described by Owen.[5] He takes the first appearance of pink colour as the end-point in the reaction, and he says that decolorisation in adults is usually finished within 100 min., with a normal upper limit of 140 min.

These earlier papers in *The Lancet* have prompted us to submit a preliminary report. As far as we know no previous investigations have studied a Scandinavian population.

We took capillary blood in the first 5 days of life. Our results are presented in the accompanying table. They suggest that the activity of G.-6-P.D. is higher in blood from adults than from infants, and that erythrocytes from newborns have less activity than those from either adults or infants. These results do not agree with those of Gross and Hurwitz [6] or of Zinkham,[7] who found more activity in blood from newborns than from adults. They used a spectrophotometric method.

Our values for enzyme activity in the " newborn " group are very scattered but seem to have a small tendency to be higher (i.e., lower enzyme activity) in the two subgroups with heavy jaundice. Doxiadis et al.[3] take no decolorisation in 180 min. as a sign that there is practically no enzyme activity, and decolorisation between 100 and 180 min. as a sign of a partial enzyme deficiency. According to these workers most of our newborns would have partial and none of them total deficiency. We cannot presumably compare their " normal " values with our results because we may not use the same criteria for estimating the decolorisation. Also we used capillary blood and they used cord blood. For the present, therefore, we usually take a value of 140 to 150 min. as the upper limit of normal in the newborn. In 4 newborn children decolorisation was incomplete in 150 min. (see table). These 4 infants with an icterus of unknown ætiology belong to the two subgroups with the most pronounced jaundice.

CASE 1.—Birthweight: 3150 g. Jaundice appeared on the fourth day. Highest serum-bilirubin level was 14·0 mg. per 100 ml. Hæmoglobin: 20·5 g. per 100 ml. Decolorisation-time: 160 min.

CASE 2.—Birthweight: 3300 g. Jaundice appeared on the third day. Highest serum-bilirubin level: 13·5 mg. per 100 ml. Hæmoglobin: 20·9 g. per 100 ml. Decolorisation-time: 160 min.

CASE 3.—Birthweight: 3280 g. Jaundice appeared on the fourth day. Highest serum-bilirubin level: 19·5 mg. per 100 ml. Hæmoglobin: 20·7 g. per 100 ml. Decolorisation-time: 160 min.

CASE 4.—Birthweight: 2750 g. Jaundice appeared on the third day. Highest serum-bilirubin level: 19·0 mg. per 100 ml. Hæmoglobin: 20·5 g. per 100 ml. Decolorisation-time: 180 min.

The neonatal period of these 4 infants was uneventful; they had no signs of anæmia or red-cell hæmolysis.

Our results do not agree with those of Doxiadis et al. It would be premature to assess the clinical value of our

1. Clark, J. A. *Lancet*, 1961, i, 618.
2. Weatherall, D. J. *Lancet*, 1960, ii, 835.
3. Doxiadis, S. A., Fessas, Ph., Valaes, T., Mastrokalos, N. *ibid.* 1961, i, 297.
4. Cited by Owen, J. A., Jr. (ref. 4).
5. Owen, J. A., Jr. *Diabetes*, 1960, **9**, 370.
6. Gross, R. T., Hurwitz, E. *Pediatrics*, 1958, **22**, 453.
7. Zinkham, W. H. *ibid.* 1959, **23**, 18.

DECOLORISATION-TIMES IN JAUNDICE

Age-group	No. of cases with decolorisation-time (min.) of										Total
	90	100	110	120	130	140	150	160	170	180	
Children and adults (3–30 yr.)	11	9	1								21
Infants (2–8 mth.)			13	3	2						18
Newborn children											
A: Dysmatures, Clifford stage I											
Serum-bilirubin, mg. per 100 ml. 0·0–12·0		1	2	5	4	2	2				16
B: Incompatibility, Rh or ABO											
Serum-bilirubin, mg. per 100 ml. <7·0			1		1						2
" " " 7·0–11·9			1								1
" " " 12·0–16·9					1						1
" " " ⩾17·0	1				1	1					3
C: Normal infants, with or without " physiological " icterus											
Serum-bilirubin, mg. per 100 ml. <7·0		2	4	2	10	3	1				22
" " " 7·0–11·9		2	3	4	8	1	1				19
" " " 11·9–16·9			5	4	5	10	1	2			27
" " " ⩾17·0	1		2	1	2	5	1	1		1	14

findings. But further studies are necessary to classify different types of neonatal jaundice.

Further investigations with Motulsky's test combined with determination of gluthatione stability are in progress.

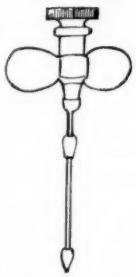
Pædiatric Department,
University Hospital,
Lund, Sweden.

G. ENGLESON
B. KJELLMAN.

A MODIFIED VENESECTION CANNULA

SIR,—We have made some modifications to our venesection cannulas to reduce their shortcomings to a minimum:

(1) A pair of wings has been placed under the hub of the cannula, these wings being gently concave downwards to conform to the contour of the limb. A small strip of sticking-plaster on each wing anchors the cannula firmly to the limb without sticking-plaster across the hub of the cannula. Better asepsis is thus achieved. The wings prevent any rotation of the cannula. At the same time, they raise the hub of the cannula from the limb and any manœuvre is easier.



(2) Usually a single bulb on the shaft, nearer the tip, is expected to keep it in the vein. Tension on the cannula—inevitable in lengthy intravenous therapy—pulls it out almost entirely, with laceration of the vein and reduction of asepsis. In our modification this bulb is placed nearer the hub so that at any time the greater part of the shaft is within the vein. A pull is less likely to dislodge the cannula out of the vein. The fluid always runs in at a distance from the site of venesection. Moreover, the bulb being close to the hub, the anchoring loop of thread hugs this bulb closely, thus reducing the leakage of fluid to a minimum.

(3) Another tapering bulb forms the tip of the cannula. This tapering bulb facilitates introduction and prevents through-and-through tears of the vein. The tip does not come in contact with the vein wall and interruption to the flow is avoided.

We have found this cannula more useful and convenient than the ordinary form.

The cannula is made by Messrs. M. Shah & Co., Bombay, 4.

K.E.M. Hospital,
Bombay,
India.

M. L. KOTHARI
B. N. IRANI
A. B. VAIDYA.

ADVERTISEMENTS FOR HEALTH

SIR,—Though one admires Dr. Mullins' unquestioned success in purchasing fruit, the question at issue remains unaltered qualitatively. It is only on the quantitative aspect that Dr. Mullins (Oct. 7) claims some concession.

She says that half an orange a day (no longer "an orange" as in her original Point of View) would cost for a family of five only about £13 per year, which is about 30% higher than the cost of all drugs under the National Health Service (not three times, as they would if oranges were bought at 4*d.* each—the figure which I used as the basis of my calculations and which is today a very usual charge in many areas). On this purely quantitative claim, I leave your readers, scattered as they are all over the country, to form their own opinions.

I would have wished to leave the matter there, but Dr. Mullins has brought in one of my own Company's products, 'Vitavel Syrup', so I feel that the record should be set straight.

The basic N.H.S. cost of 6 ounces of vitavel syrup is 2*s.* 6*d.* or of the 40-ounce dispensing size (which is what the Ministry themselves normally use for pricing purposes) 16*s.* I will, however, use the higher price. The dose is stated as 1 to 2 teaspoons a day and as Dr. Mullins has settled for half an orange a day, I will settle for the lower dose.

The hypothetical family of five will, therefore, need 35 day-doses during a week, costing approximately 1*s.* 9*d.* This compares with Dr. Mullins' own statement of 5*s.* per week for the same family using oranges, but it provides in addition 2500 i.u. vitamin A per day, equivalent to that in 3 oz. of butter or margarine, plus approximately 30% of the total vitamin B_1 requirement for the whole family, equivalent to providing each member (so far as vitamin B_1 is concerned) with 6 oz. of wholemeal bread daily.

I submit, Sir, that Dr. Mullins' suggestion that vitamin C is less expensively obtained from oranges than it is from vitamin supplements and her categorical suggestion that vitamin supplements are necessarily more expensive are misleading by being contrary to demonstrable fact.

H. C. H. GRAVES
London, W.6. Chairman and Managing Director, Vitamins Limited.

*** Readers who have been following these calculations may care to know that Dr. Mullins based her estimate on the retail price of the syrup.—ED. L.

BEHAVIOUR AND NEEDS OF INFANT MAMMALS

SIR,—Dr. Barnett's article [1] raises several fundamental questions regarding the place of man in biological taxonomy. As this point is the background of his review, closer examination might improve our understanding of the new data that recent work on laboratory animals has brought to the understanding of "internal springs of behaviour in infancy".

Dr. Barnett assumes that comparison between species is a means of getting information about one or both members of the comparison. As Meyer [2] pointed out, this method depends on idealistic morphology (type-anatomy). As types are never found in reality, their comparison gives information only about their "relation" and never about the meaning of functions and structures in the types compared, since these can be found only by studying the individual and his relations.

What is called "infancy" and "instinct" in one of the species might be found meaningless or absent in another. A premature generalisation from one species to another is not justified. Words such as species, instinct, homœostasis, drives, stimulus, and mothering are used by Dr. Barnett in describing man, without asking whether this use is tolerable in the light of what is known about man's structure and functions and without examination of their descent. The reason why Dr. Barnett discusses the notion "homœostasis" in relation to behaviour is not clear, since all his arguments confirm the fact that it is impossible to explain behaviour by homœostasis.

Portmann and his Basle school have cast serious doubt on the use of zoological terminology in anthropology. As to mothering, Portmann [3] has shown the qualitative other function of the mother-child relation in man. On this point Dr. Barnett omits a very important line of research concerning his subject. Anthropologists have recently indicated that the notions "homœostasis",[4] "living being",[5] and "species"[6] hinder the development of basic concepts about man. On the other hand, Plessner,[7] Buytendijk,[8] and others describe the animal as closed in his instincts, as a closed form (*geschlossene Form*). In this light, conceptions such as learning, intelligence, dullness, brightness, and other human characteristics used by Dr. Barnett, are inadequate to describe animals and the results of animal tests.

That Dr. Barnett's views are the heritage of some

1. *Lancet*, 1961, i, 1067.
2. Meyer, A. Logik der Morphologie. Berlin, 1926.
3. Portmann, A. Zoologie und das neue Bild des Menschen. Hamburg, 1956.
4. Gehlen, A. Der Mensch, seine Natur und Stellung in der Welt. 1940.
5. Heidegger, M. Uber den Humanismus. Frankfurt, 1949.
6. Hengstenberg, H. E. Philosophische Anthropologie; p. 346, 358. Stuttgart, 1957.
7. Plessner, H. Die Stufen des Organischen und der Mensch. Berlin. Leipzig, 1928.
8. Buytendijk, F. J. J. Mensch und Tier. Hamburg, 1958.

honourable and optimistic simplifications from the past century makes them no less fallible. Dr. Barnett uses the same words in different senses and so ends in losing "a tool of learning" in medicine and science.

Nijmegen, Holland. O. R. HOMMES.

LIPOPROTEINÆMIA IN A MALE MEDICAL AND NON-MEDICAL POPULATION

SIR,—Olson [1] included occupation as an environmental factor affecting serum levels of low-density lipoproteins which are regarded as the agent for atherosclerosis. By contrast, Gofman [2] contends that occupational stress does not raise serum lipids. Opinions also differ about the relationship of occupation to coronary-artery disease.[3 4] Gertler and White [5] conclude that coronary atherosclerosis is not confined to individuals of a particular occupational class, although those in managerial and executive positions have a relatively high frequency of this disease. It is hard to distinguish, however, between the effects of stress

SERUM-LOW-DENSITY-LIPOPROTEIN PRECIPITATE LEVELS

Age-group	Non-medical subjects			Physicians		
	Number	Mean	S.D.	Number	Mean	S.D.
20–29	146	2·7	0·7	42	2·5	0·7
30–39	166	2·9	0·9	86	2·7	0·6
40–49	95	3·0	0·7	70	3·0	0·5
50–59	44	2·9	0·6	64	2·9	0·4

associated with an executive post and those connected with attaining the responsible position. Comparison of a physician and medical-student population gave an opportunity to examine further these two effects.

Blood was collected from a group of 61 male students and 262 graduates of the same medical school. Specimens were also obtained from 451 clinically healthy males in non-medical occupations. Lipoproteins of density less than 1·063 g. per ml. were precipitated by treating 30 μl. of serum with 80 μl. of specific antiserum.[6] After centrifuging in standardised micro-capillary tubes, levels of low-density-lipoprotein-precipitate columns were measured in millimetres. Estimations made in this way have been shown to agree favourably ($r = 0{\cdot}659$) with ultracentrifugal analyses of S_f 0–400 lipoproteins.[7]

Lipoprotein-precipitate values for physicians and non-medical populations grouped according to age were strikingly similar (see table). In both groups the lowest mean lipoprotein-precipitate levels were in subjects under 30. A frequency

1. Olson, R. E. *Circulation*, 1960, **22**, 453.
2. Gofman, J. W. Coronary Heart Disease. Springfield, Ill. 1959.
3. Chisholm, B. *Scient. Amer.* 1949, **180**, 11.
4. Boas, E. P. Coronary Artery Disease. Chicago, 1949.
5. Gertler, M. M., White, P. D. Coronary Heart Disease in Young Adults. Cambridge, Mass., 1954.
6. Bergquist, L. M., Carroll, V. P., Jr., Searcy, R. L. *Lancet*, 1961, i, 537.
7. Searcy, R. L., Asher, T., Bergquist, L. M. *Clin. Chem.* (in the press).

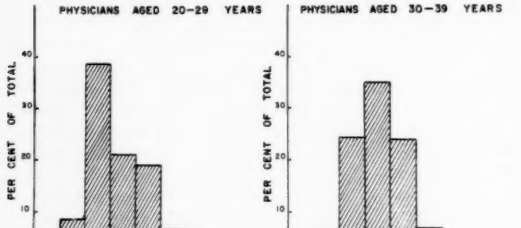


Fig. 1—Serum low-density-lipoprotein-precipitate levels in physicians under 40.

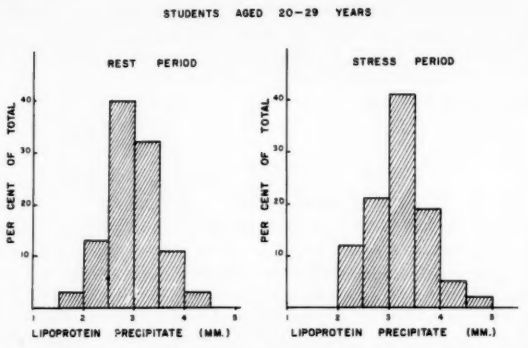


Fig. 2—Effect of examinations on serum low-density-lipoprotein-precipitate levels of younger medical students.

distribution showed that in physicians aged 20 to 29 less than 50% of the lipoprotein-precipitate values were above 2·5 mm. while 70% of those aged 30–39 had values exceeding 2·5 mm. (fig. 1). A similar trend in serum levels of S_f 0–400 lipoproteins has been observed by Gofman et al.[8] in clinically healthy males.

We have previously found that low-density-lipoprotein-precipitate levels of medical students usually increase at examination times.[9] Therefore, blood specimens were drawn from 61 students (42 aged 20 to 29, 19 aged 30 to 39) during final examinations and 3 weeks thereafter. Following the period of relative relaxation, students aged 20 to 29 and 30 to 39 years exhibited mean lipoprotein-precipitate values ($2{\cdot}9 \pm 0{\cdot}5$ and $3{\cdot}1 \pm 0{\cdot}6$ mm. respectively) which were higher than physicians of corresponding age. Moreover, student values tended to increase during the examination period (figs. 2 and 3).

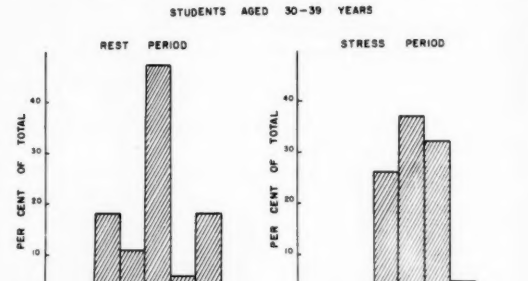


Fig. 3—Effect of examinations on serum low-density-lipoprotein-precipitate levels of older medical students.

This investigation suggests that practising physicians do not demonstrate strikingly different levels of low-density lipoproteins compared with a clinically healthy non-medical population living in the same area. Perhaps, this is consistent with the fact that physicians show no greater incidence of coronary-artery disease than individuals with other occupations.[10] It is noteworthy that on the average the medical student exhibited raised levels of lipoprotein precipitate which were augmented by exposure to examinations. Therefore, the stress involved in attaining an occupational goal may contribute to increasing low-density-lipoprotein fractions often associated with atherosclerosis.

8. Gofman, J. W., Glazier, F., Tamplin, A., Strisower, B., DeLalla, O. *Physiol. Rev.* 1954, **34**, 589.
9. Carroll, V. P., Jr., Bergquist, L. M., Searcy, R. L. *Circulation* (in the press).
10. Levine, S. A., Hindle, J. A. *New Engl. J. Med.* 1945, **233**, 657.

This investigation was supported in part by grants from the United States Public Health Service and Baxter Laboratories. Lipoprotein antiserum was generously donated by Hyland Laboratories, Los Angeles.

Los Angeles County Osteopathic Hospital, College of Osteopathic Physicians and Surgeons, Los Angeles, California.

RONALD L. SEARCY
VINCENT P. CARROLL, Jr.

ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—The point raised by Professor Holten (Sept. 23) concerning the article of Dr. Hilden and his colleagues (Aug. 12) is of considerable importance. The authors state: "The effect of anticoagulant treatment, however, cannot be expected for forty-eight hours, and for this reason we also exclude 216 patients who died within this time". Dr. Holten points out that 55 of these deaths were in the treated group (12·9% of treated patients) and 161 in the untreated group (27·5% of untreated patients). In view of this difference he questioned whether the two groups were comparable.

Examining the article by Hilden et al., it is apparent that anticoagulant therapy was started by administering 25,000 units of heparin subcutaneously twice daily until the prothrombin level dropped to below 25%. Heparin therapy of this intensity would surely exert a marked anticoagulant effect and within the first 2 hours, not 48 hours as claimed by the authors. If the two groups are comparable and if Dr. Holten's evaluation of the deaths during the first 48 hours is correct, it seems that Hilden et al. have clearly demonstrated not only the value of anticoagulant in acute myocardial infarction but also the importance of starting treatment with heparin. Since the article as it stands is open to a different interpretation, it is important that the authors present a more detailed account of the first 48 hours of treatment.

Department of Medicine, University of Toronto

J. F. MUSTARD.

DOWN'S SYNDROME

SIR,—What is Down's syndrome? It is not mentioned in the textbooks of medicine, pædiatrics, neurology, and pathology to which I usually refer. The title of the paper by Dr. Carter and Mr. Evans (Oct. 7) implies that Down's syndrome is mongolism, and mongolism is mentioned in all the books I have mentioned. Why then do Dr. Carter and Mr. Evans and Mr. Hamerton, Miss Briggs, Dr. Gianelli, and Dr. Carter (Oct. 7) not write "mongolism" if that is what they mean? It is not to encourage us to read a classic description of the disorder, for they give no reference.

Churchill Hospital, Headington, Oxford.

J. M. K. SPALDING.

SIR,—I wish to protest against the use of the term Down's syndrome in the title of two articles in *The Lancet* of Oct. 7. Why create difficulties for bibliographers, students, and all concerned? Are the authors so absolutely certain that it was Down who first described the condition? The name "mongolism" has been in use for over one hundred years and everybody knows what it implies.

London, W.1.

M. H. PAPPWORTH.

*** Our contributors prefer Down's syndrome to mongolism because they believe that the term "mongolism" has misleading racial connotations and is hurtful to many parents. Earlier this year [1] many of those engaged in research into this condition urged that "mongolism" be no longer used.[1] The term derives from Langdon Down's "Observations on an ethnic description of idiots,"[2] in which he wrote: "The great Mongolian family has many representatives." He then proceeded to give a good description of the appearance of these patients in later childhood. For these reasons we admitted "Down's syndrome" as an appropriate alternative until the chromosome abnormalities in the disorder are fully elucidated and an ætiologically descriptive name may be coined.—ED.L.

"OUTPATIENTS EXTRAORDINARY"

SIR,—Inquiries have been made about the financial arrangements for the Petworth Clinic described by Dr. Bell in your issue of Sept. 30. This is run entirely under the National Health Service without additional cost to anyone.

The letter you were kind enough to publish last week explains why the clinic is held at the practitioners' surgery. In his article, Dr. Bell explains the origin and practical details of the scheme.

All appointments are made at the general hospital, where the notes are raised, filed, the reports to the practitioners written, and the work done recorded for statistical purposes. The clinic simply becomes an extension of the outpatients services of that hospital. The physician brings and returns the notes for the clinic, and uses his own E.C.G. purely for convenience.

The general practitioners do not charge for the use of their surgery. The consultants in medicine and pathology are maximum part-time or full-time and simply had to rearrange their work to cover Petworth. They only claim mileage in the usual way. No cost falls on the hospital management committee, and they have not objected to the arrangement.

Chichester. CONSULTANT PHYSICIAN.

LUBRICATION OF JOINTS

SIR,—Professor MacConaill (Oct. 7) misleads the general reader by giving him the idea that my opinions on joint lubrication were "strongly challenged by other engineers at the time". It is true that Dr. D. Clayton, a leading authority on lubrication, did raise objections, but what was most surprising was that when the original paper was presented to the Institution of Mechanical Engineers in 1959, of the engineers his was practically the only voice against. The reply to Dr. Clayton's criticisms by Tanner and Edwards, my engineering collaborators, showed that Clayton was under a misapprehension as to the purpose of one experiment and as to certain facts of anatomy in another. The text of this interchange can be found by anyone interested on pp. 47 and 51 of the symposium on biomechanics quoted by Professor MacConaill.

Professor MacConaill oversimplifies my opinions. While I believe that in joint lubrication the conditions are nearest to the phenomenon known in engineering as "boundary lubrication", I have never denied the possible existence of conditions unique to animal joints and unknown in engineering. Indeed it was my use of the word "sponge" in relation to articular cartilage, and the reporting of my observations that viscid fluid can be expressed from articular cartilage, which started McCutchen on his studies of "weeping lubrication", as is evident in the acknowledgment of my work by McCutchen in his notice published later in *Nature*.

1. *Lancet*, 1961, i, 775.
2. *London Hosp. Rep.* 1866, **3**, 259.

While I have always been prepared to accept a compromise between pure boundary lubrication and some unique phenomenon of slipperiness as a property of semi-solids such as gels, I am not prepared to concede that any theory of full film lubrication will ever explain the conditions existing in an animal joint. Full film lubrication cannot lead to any practical application in the surgical reconstruction of a weightbearing joint and, as far as I can detect in the foreseeable future, the only successful reconstruction will be dependent on the theory of boundary lubrication with possibly some admixture of very thin fluid films.

Manchester, 3. JOHN CHARNLEY.

POSTNATAL EXERCISES

SIR,—It was precisely the advice stated in your note of Oct. 7 (p. 833)—advice which is given in numerous pamphlets and by those inexperienced in exercise therapy—that led the Obstetric Association of Chartered Physiotherapists, encouraged by several obstetricians, to produce the booklet *Your Baby and Your Figure*.

The two exercises—(1) lying on the back and lifting both legs from the bed and lowering them slowly; and (2) lying on the back " bicycling " with both legs raised in the air—are too strenuous for the majority of women during the first six weeks after childbirth. The abdominal muscles lack the strength to resist the forward pull on the lumbar spine by the hip flexor muscles when both legs are raised from the lying position. These two exercises may and frequently do cause a lengthening of the rectus abdominis muscles and unnecessary stress on the lumbar spine. Overstrain is demonstrated by muscular quivering, the held breath, bulging of the abdominal wall, and even complaints of backache. The correct method of strengthening stretched and weak muscles is to contract them fully, maintain the shortened position for a few seconds, and then to relax.

It is true that some mothers can safely progress to stronger exercises within the six weeks' period, but we believe that they can only safely do so under the supervision of a person qualified to guide the speed of progression. Stronger exercises were therefore not included in this booklet, the purpose of which is to provide a scheme of postnatal exercises which can be readily understood and carried out when a physiotherapist is not available.

MARGARET WILLIAMS
Chairman
MARY PHILLIPS
Hon. Secretary
The Obstetric Association of Chartered Physiotherapists.

PROTEIN SYNTHESIS

SIR,—In your annotation [1] on this subject some pertinent information on the " messenger " or soluble ribonucleic acid (SR.N.A.) might have been added since it was available in the references cited. SR.N.A. has a terminal nucleotide sequence of cytidyl-cytidyl-adenyl (C-C-A) and this seems to be common to all sources so far examined.

This is the type of " functional sequence " which apparently transcends species difference, to which I alluded in the last paragraph of my letter of Aug. 12 as probably being common to myceliated molds and mold-like bacteria. Or, as a matter of fact, to any cell which is capable of carrying out " instruction " for differentiation.

There is only a 50% chance that C-C-A is a linear sequence. If it could be demonstrated in D.N.A. we would know that it must be a " line of nucleotides " and in that manner might furnish a key for " cracking " the code of information furnished by polynucleotides. Occurring as it does, however, in a pentose-sugar nucleotide which is capable of branching, it may not constitute such a key.

There is more than one way to decipher a code, however, and I might remark in that connection that information theory implies the presence of similar determinative sequences common to practically all sources of D.N.A. One consequence of this deduction is the possibility of interspecies " transduction " or the use of oligonucleotide fragments from one species to cause transformations in others. This now seems to be happening continuously within the intestinal bacterial flora (either with or without the intervention of lysogenic phages) and the best explanation that we have of the growth-promoting effects of certain antibiotics is that of " host-cell transductions " by nucleotide sequences absorbed from the intestinal tract.

The other consequences of this idea—that there are common information sequences of nucleotides, capable of transferences not only within species (as in the classic transformation of R to S type pneumococci) but between species—are easily left to the imagination. Without trying to analyse these consequences it is still possible to compare the impact of a theory of interspecies transformation on the biological sciences to that of relativity and quantum theories on the physical sciences.

New York. ROBERT D. BARNARD.

1. *Lancet*, 1961, i, 1333.

SERUM-URIC-ACID IN PORPHYRIA

SIR,—Delta-aminolævulinic acid (D.A.L.A.) can participate as an intermediate in the formation of vitamin B_{12},[1] ketoglutaric compounds, and purines,[2 3] as well as porphyrins. Abnormalities in purine metabolism and uric-acid excretion and synthesis have been described in porphyria,[3] and porphyria may possibly be a " purine-deficiency " disease. It occurred to us that if a patient with porphyria (mixed or acute) were given a potent uricosuric drug the D.A.L.A. might be diverted away from porphyrin synthesis.

Six patients with porphyria were selected (one whose brother had gout!) for investigation, and it was a surprise to find that two had control uric-acid blood levels varying from 1 to 2 mg. per 100 ml., with no increase in urinary uric-acid excretion. Zoxazolamine (' Flexin ') produced a reduction in the blood-uric-acid in all of these patients but none had an alteration in porphyrin excretion or clinical status.

Several observations in the literature make this finding all the more interesting though no better understood: patients with some aminoacidurias (Wilson's disease, Fanconi's syndrome) have hypouricæmia [4]; abnormal aminoaciduria has been described in acute porphyria [5]; iron-porphyrin compounds catalyse uricolysis (slightly but definitely) in man [6]; and urinary uric acid may form a complex with porphobilinogen and inhibit its subsequent conversion to porphyrins upon heating in an acid medium.[7]

A survey of all uric-acid determinations over a four-month period in our County Hospital was undertaken. Sixteen patients were identified who had a serum-uric-acid of 2 mg. per 100 ml. or less. Fifteen were female and one male. The male was the only patient receiving a uricosuric drug. Of the fifteen females, five had had admissions to the hospital with unidentified illnesses variously described as neuroses, abdominal pain of undetermined cause, and essential hypertension. Subsequent investigation of these five patients has indicated that the most likely diagnosis was acute intermittent porphyria.

Department of Medicine,
University of Miami School of Medicine,
Miami. EMIL P. TAXAY.

1. Schwartz, S., Ideka, K., Miller, I. M., Watson, C. J. *Science*, 1959, **129**, 40.
2. Shemin D., Russel, C. A. *J. Amer. chem. Soc.* 1953, **75**, 4874.
3. Labbe, R. F., Tolman, E. L., Aldrich, R. A. *Fed. Proc.* 1955, **14**, 241.
4. *Amer. J. Med.* 1959, **28**, 614.
5. Mellinkoff, S. M., Halpern, R. M., Frankland, M., Greipel, M. *J. Lab. clin. Med.* 1959, **53**, 358.
6. Howell, R. R., Wyngaarden, J. B. *Clin. Res.* 1959 **7**, 257.
7. Watson, C. J. *Advanc. intern. Med.* 1954, **6**, 235

"TRANSLOCATED MONGOLOIDS"

Prof. ARTHUR G. STEINBERG writes:

"My colleagues, Dr. M. Neil Macintyre and Dr. William I. Staples, and I are, at present, studying three generations of a large kindred in which mongoloid offspring with translocated chromosomes have occurred. The translocation has been traced through all three generations in two families of the kindred. In preparing this material for publication we should like to summarise the data from as many families of 'translocated mongoloids' as possible to help answer some theoretical questions. We request, therefore, that investigators send us (at Western Reserve University, Cleveland 6, Ohio) reprints of their published papers and pedigrees, and summaries of the pedigrees of families they have studied but have not reported on. The source of material will, of course, be acknowledged."

Obituary

LAMBERT CHARLES ROGERS

C.B.E., V.R.D., Hon. M.D. Melb., M.Sc. Wales, F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S.

Prof. Lambert Rogers, director of the surgical unit of the United Cardiff Hospitals, died in his car on the way home from a medical meeting on Oct. 10. He was 64 years of age.

He was born in Melbourne and received his early education there, but he came to London to study medicine. He had only just joined the Middlesex Hospital Medical School when the 1914–18 war began, and he left almost at once to serve for several years with the Australian Naval Transport Service. In 1917 he returned to the Middlesex, and in 1918 he became a surgeon probationer in the Royal Naval Volunteer Reserve. He was with the Grand Fleet until demobilisation, and he first visited Cardiff when the destroyer in which he was serving docked there during the war.

Elliott & Fry

After qualifying in 1920 he was a house-surgeon to Sir John Bland-Sutton and then spent some years as a ship's surgeon and in visiting surgical clinics in the United States and in Europe. In 1926 he was appointed the first full-time assistant in the surgical unit of the Welsh National School of Medicine at Cardiff, and in due course he became senior assistant and assistant director of the unit. In 1934 he left Cardiff to become reader in surgery under Grey Turner at the Postgraduate Medical School at Hammersmith, but a year later he returned to Cardiff to succeed his old chief, A. W. Sheen, in the chair of surgery. During the late war Lambert Rogers again served with the Royal Navy, this time as surgeon captain.

From his early surgical days he was drawn to neurosurgery, and he was a pioneer of this specialty in Cardiff. He was later consultant in neurosurgery to the Royal Navy. He made a special study of the spine and spinal tumours, and much of his published work dealt with this branch of surgery and with his operation for the treatment of cervical spondylosis. He also edited many editions of Treves's *Surgical Applied Anatomy* and the fourth edition of Grey Turner's *Modern Operative Surgery*.

Professor Lambert Rogers travelled widely and since 1947 had been the British delegate to the International Society of Surgery. At Dublin this year he had been elected a vice-president and was to have been in the chair at the forthcoming meeting in Rome. He received the honorary degree of M.D. from the University of Melbourne on a visit to Australia in 1952. He was a fellow of four colleges of surgery but it was, of course, the English college with which he was most closely associated. Soon after he qualified he had worked there as a prosector in anatomy. Later he gave Hunterian, Bradshaw, and Arris and Gale lectures, and Arnott demonstrations. He served on its court of examiners and on its council, and from 1953 to 1955 was one of its vice-presidents.

A. S. D. writes:

"Apart from a year at Hammersmith, Lambert Rogers had been on the staff of the Welsh National School of Medicine since 1926 and, though an Australian by birth, he had identified himself with medicine in Wales and had played an important part in the growth of our young medical school. For six years in the war he served with great distinction in the Royal Navy, and many medical men had reason to be grateful for his help and advice with difficult neurosurgical problems. He retained a keen interest and affection for the Service. As a surgeon he gained international repute and honours; as a man he was loved by us all and his integrity and sense of duty will long be remembered."

Writing as a colleague and a friend, W. P. sends these personal words:

"Lambert Rogers' outstanding qualities as a man—complete, crystal-clear, almost childlike integrity, sincerity, consideration for others, and loyalty—were apparent to everyone whom he met even almost casually. His loyalty was tremendous and all-embracing—to surgery, to his medical schools, to the Royal College of Surgeons (and to those Royal and other Colleges of Surgeons outside England who honoured him), to all his old students and house-surgeons, and perhaps above all to his assistants and those who had taught him. He was a religious man. He observed in scrupulous detail the terms of the Hippocratic oath. His loyalty once given could not be shaken by any kind of development, and his views on the superiority of the pre-war Rolls-Royce car were as sincere as they were a little uncritical. It was typical that his last speech, at the meeting of the Cardiff Medical Society on the way home from which he died, should have been a graceful and sincere tribute to his senior surgical colleague who had just delivered a presidential address. His last important lecture was a tribute to Grey Turner, whom he regarded highly. Throughout his teaching it was apparent that his regard for the work of the surgical giants among his predecessors was no greater than his delight in acknowledging good or outstanding work by his friends and contemporaries."

Prof. Lambert Rogers leaves a widow, a daughter, and a stepson.

EDWARD FARRAR SOOTHILL

M.A., M.Chir. Cantab., F.R.C.S.

Mr. E. F. Soothill was killed in a road accident in Melbourne on Sept. 29, just after he had arrived in Australia to take up an appointment at Prince Henry Hospital, Sydney.

The son of the medical officer of health for the City of Norwich, he was born in 1923 and educated at the Leys School and Christ's College, Cambridge, where he took the natural sciences tripos in 1945. He went to Guy's Hospital and qualified in 1948, proceeding to M.A. a year later. He held house appointments at Guy's before his National Service in the R.A.M.C. The larger part of his service was spent in the thoracic unit at Cowglen Hospital, Glasgow, where he was graded junior specialist in medicine. He later returned to Guy's, and then became deputy R.S.O. at St. John's Hospital, Lewisham, where he finally decided to specialise in surgery. He became junior assistant to the surgical unit at the London Hospital, and while

there, in 1954, he took the F.R.C.S. After registrar appointments at the West Middlesex Hospital, Guy's, and Poplar Hospital, he was appointed in April, 1957, senior surgical registrar to the Norfolk and Norwich Hospital. During his time in Norwich, in 1960, he obtained the Cambridge mastership, and he wrote papers on obturator hernia and on closed traumatic rupture of the cervical trachea.

He resigned from the Norfolk and Norwich Hospital in August, 1961, on being appointed senior surgical registrar, with a view to a permanent post, to the Prince Henry Hospital, Sydney, the teaching hospital of the new University of New South Wales. He was on his way to take up this post, travelling as a ship's surgeon, when the tragic accident happened, almost immediately after he had set foot in Australia.

He had wide interests outside surgery, and that nearest to his heart was music. He was an accomplished pianist and for a number of years an active member of the Bach Choir in London. During his time in Norwich he sang regularly in the chorus of the Norwich Philharmonic Society.

In 1953, he married Elizabeth Lazenby, and they have three children.

A memorial service for Sir Bentley Purchase will be held in the Temple Church, London, E.C.4. at 4.30 P.M. on Tuesday, Oct. 24.

Public Health

Poliomyelitis in Hull

LAST April the Joint Committee on Poliomyelitis Vaccine advised the Minister of Health to keep a stock of oral vaccine ready for emergency use in an area where poliomyelitis became or showed signs of becoming prevalent. The recent outbreak in Hull was still spreading at the beginning of this week and was judged to be such an emergency. A programme of oral immunisation was therefore planned, and began last Tuesday. The aim was to give one dose of a type-2 oral vaccine to as many of the population as possible within a few days, and 51 emergency clinics were set up. They were staffed by volunteers, mostly members of the Women's Voluntary Services. On Tuesday the number of cases in Hull was reported to have reached 46, with 4 suspected cases under observation.

Appointments

DEW-JONES, J. A., M.R.C.S., D.P.M.: senior assistant psychiatrist, (S.H.M.O.), Carlton Hayes Hospital, Narborough, Leicester.

SERIGHT, WILLIAM, M.B. Glasg., F.R.C.S.E.: consultant surgeon, Dumfries and Galloway Royal Infirmary and associated hospitals.

Birmingham Regional Hospital Board:

ATKINSON, MICHAEL, M.D. Lond., M.R.C.P.: consultant physician, South Worcestershire hospital group.

CHADFIELD, H. W., M.R.C.P.: consultant dermatologist, West Bromwich, Wolverhampton and Dudley and Stourbridge hospital groups.

ENTWISTLE, CHARLES, M.B. Birm., D.P.M.: consultant psychiatrist, Birmingham (Mental B) hospital group for duties at Rubery Hill Hospital.

HANNAH, L. G. W. J., M.B. Lond., D.P.M.: consultant psychiatrist and deputy medical superintendent, Birmingham (Mental E) hospital group.

HUTCHINSON, J. A., M.B. Birm., D.P.M.: consultant psychiatrist, North Staffordshire (Mental A) and Stoke-on-Trent hospital groups.

ORWIN, ARNOLD, L.R.C.P.E., D.P.M.: consultant psychiatrist, Birmingham (Mental B) hospital group for duties at Rubery Hill Hospital.

WOOD, S. R., M.B. Birm., M.R.C.P.: consultant dermatologist, South Worcestershire and Birmingham (Dudley Road) hospital group.

Liverpool Regional Hospital Board:

FORSTER, J. E., M.D. Cantab., M.R.C.P.: consultant physician, Southport hospital group.

GALLOWAY, R. W., M.D. Lpool., D.OBST., D.M.R.D., F.F.R.: consultant radiologist, St. Helens and Warrington hospital groups.

GRAHAM, H. A. P., M.B. Durh., F.F.A.R.C.S., D.A.: consultant anæsthetist, Birkenhead and North Wirral hospital groups.

MARTIN, L. G. C., M.B. Lond., F.R.F.P.S., M.F. Hom.: consultant homœopathic physician, Liverpool Homœopathic Hospital.

READETT, M. D., M.B. Birm., M.R.C.P.: consultant dermatologist, Broadgreen and Newsham General Hospitals.

ROBINSON, J. S., M.D. Lpool., F.F.A.R.C.S., D.A.: consultant anæsthetist, St. Helens hospital group.

Notes and News

APPROVED NAMES FOR DRUGS

The British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Ampicillin	6-[(-)-α-Aminophenylacetamido]penicillanic acid [(-)-α-Aminobenzyl]penicillin Penbritin
Benzphetamine	*N*-Benzyl-*N*α-dimethylphenethylamine Didrex is the hydrochloride
Butylated Hydroxyanisole	A mixture of 2-*tert*.butyl-4-methoxyphenol and 3-*tert*.butyl-4-methoxyphenol
Butylated Hydroxytoluene	2:6-Di-*tert*.butyl-*p*-cresol
Droxypropine	1-[2-(2-Hydroxyethoxy)ethyl]-4-phenyl-4-propionylpiperidine
Nicocodine	6-Nicotinoylcodeine
Oxethazaine	2-Di-(*N*-methyl-*N*-phenyl-*tert*.butylcarbamoylmethyl)-aminoethanol
Piritramide	4-(4-Carbamoyl-4-piperidinopiperidino-2:2-diphenyl-butyronitrile
Plasmin	The proteolytic enzyme derived from the activation of plasminogen Actase is Plasmin (human)
Propicillin	6-(α-Phenoxybutyramido)penicillanic acid (1-Phenoxypropyl)penicillin Brocillin is the potassium salt; Ultrapen is the potassium salt
Rifomycin	Antibiotics isolated from a strain of *Streptomyces mediterranei* (specific substances are designated by a terminal letter; thus, Rifomycin B)
Syrosingopine	Methyl 18-(4-ethoxycarbonyloxy-3:5-dimethoxybenzoyl)-reserpate Singoserp
Tolpropamine	*NN*-Dimethyl-3-phenyl-3-*p*-tolylpropylamine
Troxonium Tosylate	Triethyl-2-(3:4:5-trimethoxybenzoyloxy)-ethylammonium tosylate (Tosylic acid is the trivial name for *p*-toluenesulphonic acid)
Troxypyrrolium Tosylate	*N*-Ethyl-*N*-2-(3:4:5-trimethoxybenzoyloxy)-ethylpyrrolidinium tosylate (Tosylic acid is the trivial name for *p*-toluenesulphonic acid)
Vinblastine	An alkaloid extracted from *Vinca rosea* Velbe is the sulphate

Proprietary name	*Approved name*	*Proprietary name*	*Approved name*
Actase	Plasmin	Singoserp	Syrosingopine
Brocillin	Propicillin	Ultrapen	Propicillin
Didrex	Benzphetamine	Velbe	Vinblastine
Penbritin	Ampicillin		

LEARNING IN SLOW MOTION

LEARNING is a simple word for the complex processes by which various aspects of behaviour are modified or reinforced throughout life. By these processes man is able to profit from years of human experience during his relatively short period of development. Almost every dimension of behaviour—thinking, perceiving, working, and so forth—has some learned component, and thus investigation of learning processes is essential to our understanding of human behaviour.

The mentally subnormal, almost by definition, have learning difficulties, usually in the form of slowness and impairment of range. Yet essentially their methods of learning are similar to those of others. By their very simplicity, however, these processes appear in sharper relief and hence can be more easily identified and analysed. Research on how the mentally subnormal learn is, therefore, likely to have some implications for normality, and its investigation suggests how limited assets may be developed in the interests of the patient and of society.

The film *Learning in Slow Motion*,[1] made at The Manor Hospital, Epsom, is divided into two parts.

The first is concerned with the subnormal, and in particular with the least fortunate of these—that is, those with backgrounds of social adversity and poor psychological assets in adolescence. The earlier instability of many of them is exemplified by a former patient discussing his one-time difficulties. These patients are shown in various stages of industrial training. The procedure of their placement in normal industrial jobs in the community is demonstrated, and a foreman testifies to their capabilities and adaptability in a large television factory. In brief, under conditions of full employment, and with realistic training, the minority of subnormals who need hospital

1. *Learning in Slow Motion: a Record of Research on Subnormality*. Black and white, 16 mm., sound, 30 min. Data Film Productions Ltd. Inquiries should be addressed to the Group Secretary, Manor Hospital, Epsom, Surrey.

care can usually achieve the goal of independence, and learn to function as well as their more fortunate peers.

The second part of the film shows that the abilities of most of the severely subnormal (those who, in older parlance, were termed "imbeciles") have been considerably underestimated. Laboratory and workshop studies combine to indicate, surprisingly, that, despite gross impairment, much can be done for them, and that on simple industrial work these persons can usually achieve normal speeds and quality under sheltered conditions. Moreover, learning one task facilitates learning others of a similar nature. This is particularly evident in severely subnormal children. Accordingly, it seems that the revival of realistic "sense-training" techniques is vitally important.

Severely subnormal patients are shown in their normal hospital background and in various stages of learning both laboratory and workshop tasks. Their gross inadequacy (often incorrectly interpreted as *inability* to learn) at the start of the learning process is contrasted with their deft and accomplished performance some time later. It is suggested that such persons are both happier and of greater use to society in undertaking real productive work, for which they are paid, than in being merely "occupied".

To sum up, this film attempts to demonstrate the value of experimental method in analysing the learning problems of all types of subnormals, and in devising training techniques to overcome these problems.

University of London

The diploma in clinical pathology has been granted to the following:

W. de C. Baker, A. J. C. Balfour, Helen V. Bashir, L. D. Berman, C. G. Berry, Betty Chu, R. V. P. Dissanayake, Ahmed Mohmed El Hassan, D. O. Haines, Anita M. Herdən, Maung Ko, Aderohunmu Oladipo Laja, Sheila I. Macvie, V. I. Massiah, S. T. H. H. Pilbeam, C. M. D. Ross, Sri Krishan Saigol, Kheng Khoo Tan, N. E. Traub, J. D. Williams.

University of Bristol

Six lectures on current topics in psychiatry are to be given at 8.30 P.M. on certain Thursday evenings. The first, on the borderland between functional and organic mental illness, will be given at the Queen's Buildings, University Walk, on Oct. 26 by Dr. Martin Roth, professor of psychological medicine in the University of Durham.

University of Aberdeen

Dr. Eric McKay has been appointed lecturer in child health, and Dr. K. J. Dennis lecturer in midwifery and gynæcology.

Royal College of Surgeons of England

At a meeting of the council on Oct. 12, with Sir Arthur Porritt, the president, in the chair, the Hallett prize was presented to Miss I. Sri Skanda Rajah (Ceylon) and Handcock prizes to Dr. J. B. Brown and Dr. N. K. Coni. Diplomas of fellowship were granted to M. A. Ilahi and T. Coetzee, diplomas of fellowship in the Faculty of Anæsthetists to M. Evans and J. D. Hill, and diplomas of membership to J. B. Brown, A. J. Marengo-Rowe, and F. M. Barrett. The following diplomas were granted, jointly with the Royal College of Physicians:

D.O.—Soli Dara Adrianwala, Mira Khan Afridi, Busharat Ahmad, Iqbal Ahmad, Syed Anwer Ali, Mounir Mohamed Osman Beiram, G. H. Bevan, Samir Kumar Biswas, J. F. Bras, Anne E. Clancy, Iswari Anmal Coomaraswami, J. B. Cowle, J. F. Crewdson, E. R. Dingley, M. M. S. du Toit, E. R. Earnshaw, Moinul Haq, Margaret M. Harkness, J. R. Hawkins, F. C. Hollows, Sami Noah Jebri, Kochukalikal John Kurian, Shanker Mandalaywala Lal, G. J. B. Leslie, A. L. McKay, C. J. F. Maguire, Niranjan Singh Mangat, Hemchandra Kanjibhai Mehta, Mahmoud Waguih Nafie, Surendra Shahu Nawgiri, G. K. Nixon, W. O. Petrie, P. W. Pitt, Dorothy M. Rees, B. A. Rodan, H. M. Rose, Rasiah Sivagurunathan, Ponniah Sivaraja, J. M. Smail, V. H. Smith, J. T. Snow, Krishan Gopal Soni, Suzanne R. Veronneau, W. D. Waller, J. P. B. Walsh, John Williamson, James Winning.

D.T.M. & H.—Peter Abraham, Babatunde Kwaku Adadevoh, Abdul Muttalib Abdul Razzak Al-Mahdi, Jane Anwan, Jayantilal Jessang Arya, S. E. Augustt-Moffatt, Myint Myint Aye, Arthur Banks, Mohan Kumbla Bhakta, Gopinath Gopal Bhure, Cyrus Borbor, P. R. Brown, Danai Bunnag, Raymond Carlisle, Termsri Chomnijarakij, W. M. Cornelius, Jawahir Lal Dhar, F. M. Dourado, D. R. Gunraj, Barun Kumar Gupta, Omar Hamid, J. R. Harrison, J. G. Holmes-Smith, Tara Kant Jha, Evelyn M. M. Jones, Anna-Stina Jonsson, R. W. W. Kay, D. H. McFerran, Tin U Maung, T. M. Moles, A. D. Moore, Ole Halgrim Evjen Olsen, G. W. Peacock, Sabah Hanna Petros, Om Prakash, Raghavendra Prasad, Abul Qusaem Badiur Rahman, Gopal Rakshit, Madhukar Pradyumna Rele, R. G. Robinson, Krong Sangsilapa, Kantilal Ishwarlal Shah, A. J. Shaw, Zia-ur-Rehman Siddiqi, R. C. Stewart, P. M. Stoker-Murdy, Rudrapatna Srinivasiah Subhanna, Donna Man-Kiu Tang, Tun Thin, Svein Tjaland, Hla Tun, M. B. Watts, M. C. Wotton.

D.C.H.—Narendra Kumar Agarwal, Qutub Uddin Ahmed, Tofayel Uddin Ahmed, Rachad Anbari, Ann D. Banister, Janet I. Beggs, D. R. Benady, Indra Bhatia, Sybil Birtwistle, Alice M. Bradley-Moore, M. F. H. Bush, Nirmal Chander, Pritikana Chattopadhyay, Kim Hoe Chee, Ruth Chenoweth, Gillian A. Clarance, Jennifer P. Cruthers, Lakshminarayanapuram Vishwanathan Devarajan, Abbas Hasanally Dossal, Julia P. Ellis, Madhusudan Shivaji Erram, Rachel G. Evans, Mohomed Nabih Ahmed Farhat, Anne A. Ferry, I. I. Findlay, D. H. Fox, Bernadette A. Gallagher, Louise Gallagher, J. W. Gibson, Lenore Z. Gladstone, R. J. Golding, Llewellyn Samarasinha Gunasekera, D. R. Gunraj, Elise M. Hendry, Judith M. Heron, J. A. Hill, J. D. Hobday, E. J. Housley, J. M. Howell, Rosemary A. Hunt, P. B. Jacobs, Beryl I. E. Jones, W. G. G. L. Jones, Savitri Kasemsri, J. A. Keipert, Patricia A. Kent, Khin Myo Win, Adisesha Gopal Krishna Veerandra Kumar, Patricia O. Lane, Elizabeth R. Lohoar, Mary K. Lucas, B. W. M. Macartney, Robert MacLennan, Rae N. Matthews, Thein Thein Myint, Bala Krishna Hareendran Nair, Kamalini Narayan, Nwabuoku Egemonye Okoye, Badri Raj Pande, Saroj Ranchhoddas Parekh, Vithalbhai Ranchhodbhai Patel, Nomal Chandra Pegu, H. J. Phillips, Salvatore Raiti, C. A. Ramsay, Premchand Narpat Ratan, Aileen O. B. Redmond, C. A. Reindorf, Sureshchandra Raghunath Rele, Doris E. Ribeiro, Shirley J. Richards, Jane C. H. Richings, R. R. Roberts, Alfred Robinson, J. R. Robinson, Peter Robson, Olumuyiwa Seriki, Meenakshi Mugatlal Shah, Dinesh Chandra Sharda, Arthur Sothyrajan Sinnatamby, Marguerite E. Smith, Jagmohan Ram Srivastava, Hans Steiner, Joan Stephenson, E. P. W. Tatford, Henry Teed, Sheila Thambiah, Ambalavana Kanapathy Thambiran, Dorothy E. A. Thompson, Sylvia G. Thornicroft, Chandra Mouli Tiwary, Winifred M. M. Tully, I. W. Wallace, Pamela Walton, A. F. Watson, Corinna M. Weaver, Anne G. Wesley, Mary K. West, Margaret J. Wharton, D. M. Whiteford, A. S. Wilson.

D.Phys. Med.—L. G. Andrews, J. F. M. Bartholomeusz, Ma Khin Kyi, Olwen V. Rees, C. D. Waltham-Weeks.

D.L.O.—G. Mervis, K. J. Singh.

Prof. Digby Chamberlain will give a Bradshaw lecture on Thursday, Nov. 9, at 5 P.M., at the college, Lincoln's Inn Fields, London, W.C.2. His subject will be the spleen and its removal.

University College of East Africa

Dr. David Allbrook has been appointed to the chair in anatomy at Makerere College.

Association of Clinical Biochemists

The following officers have been elected:

President, Dr. A. L. Latner; chairman, Mr. H. Varley; hon. treasurer, Dr. R. Gaddie; hon. secretary, Dr. J. H. Wilkinson (Westminster Medical School, Horseferry Road, London, S.W.1).

World Health Organisation

Dr. Oganes Vagarshakovich Baroyan has been appointed an assistant director-general of W.H.O.

Dr. Baroyan, who was born at Erevan, Soviet Armenia, in 1906, comes to Geneva from Moscow where he directed the Gamaleya Institute of Epidemiology and Microbiology, with a staff of 1700.

Society of Chemical Industry

The nutrition panel of this society is to hold a series of meetings on manufactured foods in the dietary control of disease. The first of these meetings will be on Wednesday, Oct. 25, at 6.15 P.M., at 14, Belgrave Square, London, S.W.1, when the subject will be foods low in salt. The programme will include a paper by Prof. D. A. K. Black on the clinical uses of low-salt diets.

International Psychosomatic Cancer Study Group

This group held its second international conference in Paris on Aug. 27–29, when about 30 representatives from ten countries attended. Among those reading papers were Dr. J. G. Henderson, Dr. I. Frost, and Dr. D. M. Kissen; and Dr. S. Feigenberg led a discussion on the possibility of introducing a psychological service to aid the cancer specialist in the treatment, care, and rehabilitation of the cancer patient. Abstracts of the papers may be had from Dr. Kissen at Brookfield, Elm Walk, Bearsden, Glasgow.

Central Middlesex Hospital

As the first stage of a scheme by which this hospital will have a new outpatient and casualty department, and the X-ray and pathology departments will be extended, a new block was opened on Oct. 5.

On the ground floor this has 4 consulting suites, each with 2 consulting-rooms, 2 examination rooms, undressing cubicles, and a nurses' station. There is also additional waiting space and the usual ancillary offices. The first floor accommodates a bacteriology laboratory, a tuberculosis laboratory, a biochemistry laboratory, the blood-transfusion department, and a hæmatology laboratory, together with offices and a consulting-room.

The cost of the block has been about £116,000 and the cost of its equipment is estimated at nearly £16,000.

Ciba Foundation Lecture

Prof. E. Katchalski of the Weizmann Institute of Science, Rehovoth, will give a lecture on Monday, Nov. 20, at 5 P.M., at the Royal Institute of British Architects, 66, Portland Place, London, W.1. His subject will be synthetic macromolecules as protein models. Tickets may be obtained from the assistant secretary of the Foundation, 41, Portland Place.

Diseases of Genetic Ætiology

A conference on this subject is to be held by the Glasgow Postgraduate Medical Board, University of Glasgow, and the Royal Faculty of Physicians and Surgeons from Nov. 15 to 17 at the hall of the Faculty, 242, St. Vincent Street, Glasgow, C.2. Further particulars will be found in our advertisement columns.

Central Council for Health Education

The annual conference of this Council will be held on Thursday, Jan. 25, at 10 A.M., at the National Film Theatre, London, S.E.1. The theme of the conference will be Parents and Children. Further particulars may be had from the medical director of the Council, Tavistock House North, London, W.C.1.

Association of Anæsthetists of Great Britain and Ireland

A scientific meeting for registrars is to be held by this Association on Friday, March 20, in Manchester. Further particulars may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

British Association of Sport and Medicine

A joint meeting of this Association and the Ergonomics Research Society is to be held on Saturday, Oct. 28, at 10 A.M., at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.

Association of Industrial Medical Officers

A meeting of this Association will be held on Friday, Oct. 27, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, and on Saturday, Oct. 28, at Westminster Hospital, Horseferry Road, S.W.1. Further particulars may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, W.C.2.

Biochemical Society

The office of this society and the editorial office of the *Biochemical Journal* will move on Nov. 4, to 20, Park Crescent, Regent's Park, London, W.1.

Pan-African Psychiatric Conference

The first Pan-African psychiatric conference is to be held from Nov. 12 to 18 at the neuropsychiatric centre, Aro Hospital, Abeokuta, Western Nigeria. It will be attended by about 150 people—psychiatrists, social scientists, public-health officers, hygienists, and medical educators—from various countries in Africa, and by representatives of international bodies. During the conference Sir Aubrey Lewis and Sir Russell Brain will hold regular clinical meetings and ward rounds at Aro Hospital.

A public meeting of the Abortion Law Reform Association is to be held at Conway Hall, Red Lion Square, London, W.C.1., on Wednesday, Nov. 1, at 7.30 P.M. This will be preceded at 6.45 P.M. by the annual general meeting.

A new and enlarged edition of a handbook for Edinburgh general practitioners summarises facilities for the care of the chronic sick, the aged, and patients with mental-health problems. It has been compiled by Dr. E. V. Kuenssberg for the local medical committee, and copies may be had from the executive council, 37a, Drumsheugh Gardens, Edinburgh, 3.

The Standing Conference of Societies Registered for Adoption have published a new edition of their booklet *Adopting a Child*, which incorporates all recent legislative changes and includes a list of all adoption societies in the United Kingdom. Copies (1*s.* post free) may be had from the hon. secretary, Gort Lodge, Petersham, Surrey.

An exhibition of documents from the hospital archives is to be held at St. Thomas' Hospital Medical School, London, S.E.1, from Nov. 14 to 17. The exhibition will be open from 11 A.M. to 6 P.M. daily.

Diary of the Week

OCT. 22 TO 28

Monday, 23rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Hypochondriasis.

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5 P.M. Prof. J. N. Davidson: Biosynthesis of Polynucleotides. (First of two lectures.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Odontology.* Prof. W. E. Herbert: Training of the Dental Surgeon. (Presidential address.)

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Odontology.* Prof. H. G. Radden: Mouth Wounds. (Presidential address.)
9 P.M. *General Practice.* Mr. A. R. Anscombe: Abdominal Pain.

Tuesday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. A. J. M. Reese: Tumours of the Kidney. (Erasmus Wilson demonstration.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. L. Brent: Current Problems in Transplantation Immunity.

ROYAL SOCIETY OF MEDICINE
8 P.M. *Medicine.* Dr. A. M. Cooke: The Art of Making Mistakes. (Presidential address.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Sir Andrew Claye: Disturbances of Sexual Function.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. E. H. Larkin: Drug Treatment in Psychiatry.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. A. G. W. Whitfield: Pulmonary Fibrosis.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Mr. Frank Nicholson: Napoleon and his Doctors.

Wednesday, 25th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. D. H. Tompsett: Casts of the Bronchial Tree. (Arnott demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. M. D. Milne: Renal Function Tests.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Dr. W. J. Schindler (Texas), Dr. I. C. Gilliland, Dr. M. B. Ghose, Dr. B. Davies: Control of Pituitary Function.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Prof. C. D. Calnan: Physiology of Itching.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. R. V. Gibson: Constrictive Pericarditis and Cardiac Tamponade.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Prof. J. V. Dacie: Apsects of Hæmolytic Anæmias.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. J. N. Walton: Current Concepts of Muscle Disease.

Thursday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Sir Clement Price Thomas: Vicary amongst his Contemporaries. (Thomas Vicary lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. Henry Harris: Transfer of Information from Nucleus to Cytoplasm.

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services.* Wing-Commander P. R. Travers: Moroccan Oil Paralysis.
8 P.M. *Urology.* Mr. J. C. Anderson: Hydronephrosis—a fourteen years' Survey of Results.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Prof. A. W. Grace (New York): Microscopic Pattern of Disintegration of Nuclei in Pemphigus, Contact Dermatitis, and Disseminated Lupus Erythematosus.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Dr. R. C. Nairn: Immunofluorescence in Medicine.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.m. (11, Chandos Street, W.1.) Dr. Stuart Mason: The Hairy Woman.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Dr. H. Lehmann: Modern Developments in the Recognition of Abnormal Hæmoglobins.

Friday, 27th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. V. H. Riddell: Unsettled Thyroid Problems.
4 P.M. Prof. L. S. Penrose: Mongolism.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Mr. F. L. F. Innes, Mr. C. A. Holborow: Cleft Palate. Dr. Donald Gough: Visual Behaviour of Infants in the First Few Weeks of Life. Dr. R. E. Bonham-Carter: Indications for Cardiac Surgery in the First Year of Life.
8.15 P.M. *Obstetrics and Gynæcology.* Mr. C. M. Gwillim: A Meeting of the Royal Medical and Chirurgical Society in the Session 1861–62. (Presidential address.)

WILLIAM MACKENZIE LECTURE
5 P.M. (Royal Faculty of Physicians and Surgeons, 242, St. Vincent Street, Glasgow.) Prof. G. Meyer-Schwickerath: Management of Ocular Tumours.

CORRIGENDUM: *Partial Hepatectomy.*—In our report (Oct. 7, p. 808) of Dr. H. J. W. Cleeve's remarks on this subject the figures described as prothombin levels were in fact fibrinogen levels. We also regret that Dr. Cleeve's name was misspelt.